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**WO 02/28929 A1**

(54) **Title:** ZWITTERIONIC POLYMERS

(57) **Abstract:** Polymers may be made from zwitterionic monomers having controlled architectures and molecular weights, using living polymerisations such as group or atom transfer radical polymerisation. For instance polymers may be formed by atom transfer radical polymerisation using a copper chloride catalyst, a ligand which is water soluble, and a water soluble tertiary alkyl halide initiator to form homopolymers having controlled polydispersities of less than 1.5 and block copolymers with other hydrophilic or hydrophobic monomers. One suitable zwitterionic monomer is 2-methacryloyloxy-2'-trimethylammoniumethyl phosphate inner salt. The block copolymers may spontaneously form micelles, believed to have zwitterionic, for instance phosphorylcholine, groups at the external surface, which may be useful as drug delivery systems with improved biocompatibility.
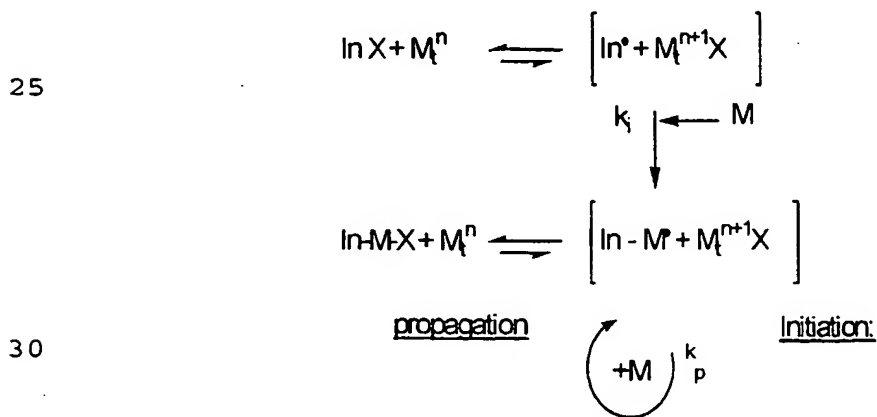
## Zwitterionic Polymers

The present inventions relates to zwitterionic polymers having controlled architectures, specifically having controlled chain length and/or block chain length in block copolymers.

5 It is known that phosphorylcholine based polymers can be used to produce surfaces which are resistant to protein adsorption and blood and microbial cell adhesion. Copolymers of 2-methacryloyloxymethyl-2'-trimethylammonium ethyl phosphate inner salt (MPC) formed by solution polymerisation using thermal initiators such as azoisobutyronitrile are

10 described in WO-A-9301221. Comonomers are selected to confer particular surface binding characteristics. · For instance hydrophobic comonomers such as $C_{8-24}$ -alkyl(meth)acrylate comonomers confer surface binding for hydrophobic surfaces. Reactive comonomers confer crosslinkability or covalent reactivity to surface functional groups. Ionic

15 monomers confer electrostatic binding to oppositely charged surfaces. Various improvements have been described, for instance cationic comonomers have been used to provide additional desirable characteristics as described in WO-A-9822516. Improved crosslinking systems are described in WO-A-9830615.

20 The mixture of MPC and comonomers in the above specifications has reactivity ratios far from 1:1. In thermal (or redox) initiated radical polymerisations, the rate of propagation is very high compared to the rate of initiation. New initiator radicals are generated throughout the course of a polymerisation. Since one of the monomers is more reactive than the

25 other(s), the composition of monomer available for polymerisation throughout a polymerisation process, and hence the composition of polymer molecules made throughout a process, varies. Whilst some compositional variation may be tolerated in some applications, and may even have benefit in terms of properties it conferred, it is often desirable to provide polymer

30 having a narrower range of composition and molecular weight.

Some improvements in the compositional variation have been described in WO-A-9822516 and PCT/GB00/02078. The polymerisations

were conducted under monomer starved conditions, by feeding a mixture of monomers over an extended period into the reaction vessel containing initiator. However these processes still produce polymers having a wide variation in terms of molecular weight (polydispersity).

5      Polymerisation methods for polymerising ethylenically unsaturated monomers to provide narrow polydispersities have been developed. One class of polymerisations use ionic living polymers. These are generally conducted in organic solvents (toluene, tetrahydrofuran) in which zwitterionic monomers, which tend to be highly hydrophilic, are insoluble. One type of

10     living polymerisation, sometimes termed pseudo-living polymerisation, developed by Matyjaszewski is called atom transfer radical polymerisation (ATRP). The process is described *inter alia* in WO-A-96/30421, US-A-5807937, WO-A-98/40415, WO-A-9807758 and US-A-5789487. All these polymerisations require a low stationary concentration of growing radicals,

15     $M_n \bullet$ , which are in a fast dynamic equilibrium with the dormant species, $M_n X$. This reduces the extent of termination reactions by two growing radicals joining together. The initiation reaction should be very fast compared to the rate of propagation. The reaction of growing radicals $M_n \bullet$ react reversibly with radicals X which, in ATRP are atoms, generally halogen atoms. In

20     ATRP, the reversible reaction involves a transition metal compound which is able to change oxidation states. The general reaction scheme of atom and group transfer may be represented as follows:

25

$$\text{In}\,X + M_t^n \;\rightleftharpoons\; \left[\, \text{In}^\bullet + M_t^{n+1}X \,\right]$$

$$k_i \,\Big\downarrow\!\!\leftarrow M$$

$$\text{In-M-X} + M_t^n \;\rightleftharpoons\; \left[\, \text{In-M}^\bullet + M_t^{n+1}X \,\right]$$

propagation                    Initiation:

30

$$\left(\, +M \,\right) k_p$$

in which InX is the initiator compound, $M_t$ is the transition metal compound, which is convertable from n oxidation state to the n+1 oxidation state, and M is the monomer. Ki is the initiation rate constant, and $K_p$ is the propagation rate constant. The reactions involving the transition metal redox cycle are reversible. The rate constants of the various reactions result in relatively low stationary levels of the moiety In-$M_n$', since this reacts to form the dormant species In-M-X. The molecular weight increases linearly with increasing monomer conversion. In ATRP, ligands are generally present to complex the transition metal ions, generally in both oxidation states.

Most of Matyjaszewski's ATRP reactions are conducted in organic solvent. Recently X-S Wang et al., in Chem. Commun., 1999, 1817-1818 and in Polymer Preprint 2000, 41(1), 413-414, describe atom transfer radical polymerisations conducted in aqueous media involving water soluble ethylenically unsaturated monomers such as hydroxy ethyl methacrylate (HEMA), sodium methacrylate, sodium 4-vinylbenzoate, 2-aminoethylmethacrylate, 2-sulphatoethyl methacrylate ammonium salt, 3-sulphopropyl methacrylate potassium salt, N-(4-vinylbenzyl) trimethyl ammonium chloride and monomethoxy-capped oligo(ethylene oxide)methacrylate (OEGMA). The initiators used were water soluble bromine substituted compounds such as the reaction product of monomethoxy-capped oligo(ethylene oxide) with 2-bromoisobutyryl bromide (OEGBr), 4-bromo-α-toluic acid or ethyl 2-bromopropanoic acid, or 2-(N,N-dimethylamino) ethyl-2'-bromoisobutyrate. The reactions could be conducted at ambient temperatures, at which conversion rates of more than 95% were obtained after less than half an hour. Block copolymers could be formed by the use of the OEGMA-derived macro initiator for polymerising 2-sulphatoethyl methacrylate. Armes described polymerisation of a carboxybetaine monomer in similar systems at a conference in Cambridge, "Controlled free radical polymerisation" 21 September 2000.
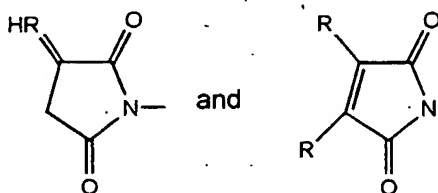
Haddleton, D.M. et al at 217th ACS National meeting, Anaheim March 21-25, 1999, POLY-024, described catalytic chain transfer (CCT) polymerisations in aqueous solutions of acrylic monomers, such as 2-

methacryloyloxy-2'-trimethylammonium ethyl phosphate, using a cobalt catalyst, cobaloxine boron fluoride. In CCTP the metal of the catalyst becomes directly joined (reversibly) to the growing polymer chain.

According to the present invention there is provided a new polymerisation process in which ethylenically unsaturated monomers including a zwitterionic monomer of the general formula I

$$Y \, B \, X \qquad I$$

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,



and

A is $-O-$ or $NR^1$;

$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n \, SO_3-$ in which n is 1 to 12;

$A^2$ is selected from a bond, $-O-$, $O-CO-$, $CO-O$, $CO-NR^1-$, $-NR^1-CO$, $O-CO-NR^1-$, $NR^1-CO-O-$;

R is hydrogen or $C_{1-4}$ alkyl;

$R^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

$R^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;
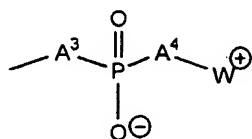
X is an ammonium, phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group,

are polymerised by a living radical polymerisation process in the presence of an initiator, and a catalyst.

The zwitterionic group X, in this aspect of the invention, comprises as the cationic moiety, and ammonium, phosphonium or sulphonium group.

Preferably the cation is an ammonium group. The anion of the zwitterion is a phospho moiety. It is generally a phosphate diester, or a phosphonate ester based moiety. Generally in the zwitterionic group X, the anion is closer to B than the cation. However in some zwitterions, the cation is closer to the group B than is the anion (called hereinafter phosphobetaines).

Preferably X is a group of the general formula II

$$\overset{\displaystyle O}{\underset{\displaystyle O^{\ominus}}{\overset{\|}{\underset{|}{-A^3}\diagdown P \diagup A^4 \diagdown_W \oplus}}} \qquad \text{II}$$

in which the moieties $A^3$ and $A^4$, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and $W^+$ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a $C_{1-12}$-alkanediyl group,

preferably in which $W^+$ is a group of formula

$-W^1-N^+R^3_3$, $-W^1-P^+R^4_3$, $-W^1-S^+R^4_2$ or $-W^1-Het^+$ in which:

$W^1$ is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group $W^1$ optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups $R^3$ are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or two of the groups $R^3$ together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups $R^3$ together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups $R^3$ is substituted by a hydrophilic functional group, and
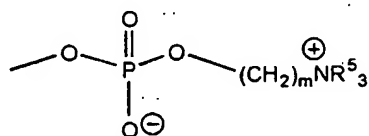
the groups $R^4$ are the same or different and each is $R^3$ or a group $OR^3$, where $R^3$ is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

Monomers in which X is of the general formula in which $W^+$ is $W^1N^+R^3_3$ may be made as described in our earlier specification WO-A-9301221. Phosphonium and sulphonium analogues are described in WO-A-9520407 and WO-A-9416749.

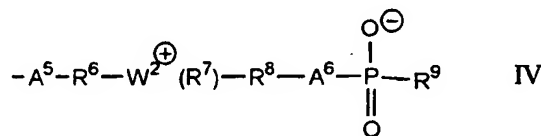Generally a group of the formula II has the preferred general formula III

$$-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^{\ominus}}{|}}{P}}-O-(CH_2)_m\overset{\oplus}{N}R^5_3 \qquad \text{III}$$

where the groups $R^5$ are the same or different and each is hydrogen or $C_{1-4}$ alkyl, and m is from 1 to 4, in which preferably the groups $R^5$ are the same preferably methyl.

In phosphobetaine based groups, X may have the general formula IV

$$-A^5-R^6-\overset{\oplus}{W^2}(R^7)-R^8-A^6-\overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\underset{\displaystyle O}{\|}}{P}}-R^9 \qquad \text{IV}$$

in which $A^5$ is a valence bond, -O-, -S- or -NH-, preferably -O-;

$R^6$ is a valence bond (together with $A^5$) or alkanediyl, -C(O)alkylene- or -C(O)NH alkylene preferably alkanediyl, and preferably containing from 1 to 6 carbon atoms in the alkanediyl chain;

$W^2$ is S, $PR^7$ or $NR^7$;

the or each group $R^7$ is hydrogen or alkyl of 1 to 4 carbon atoms or the two groups $R^7$ together with the heteroatom to which they are attached form a heterocyclic ring of 5 to 7 atoms;

$R^8$ is alkanediyl of 1 to 20, preferably 1 to 10, more preferably 1 to 6 carbon atoms;

$A^6$ is a bond, NH, S or O, preferably O; and

$R^9$ is a hydroxyl, $C_{1-12}$ alkyl, $C_{1-12}$ alkoxy, $C_{7-18}$ aralkyl, $C_{7-18}$ -aralkoxy, $C_{6-18}$ aryl or $C_{6-18}$ aryloxy group.

Monomers comprising a group of the general formula IV may be made by methods as described in JP-B-03-031718, in which an amino substituted monomer is reacted with a phospholane.

In compounds comprising a group of the general formula IV, it is preferred that

$A^5$ is a bond;

$R^6$ is a $C_{2-6}$ alkanediyl;

$W^2$ is $NR^7$:

each $R^7$ is $C_{1-4}$ alkyl;

$R^8$ is $C_{2-6}$ alkanediyl;

$A^6$ is O; and

$R^9$ is $C_{1-4}$ alkoxy.

In the zwitterionic monomer of the general formula I it is preferred that the ethylenic unsaturated group Y is $H_2C=CR-CO-A-$. Such acrylic moieties are preferably methacrylic, that is in which R is methyl, or acrylic, in which R is hydrogen. Whilst the compounds may be (meth)acrylamido compounds (in which A is $NR^1$), in which case $R^1$ is preferably hydrogen, or less preferably, methyl, most preferably the compounds are esters, that is in which A is O.

In monomers of the general formula I, especially where Y is the preferred (alk)acrylic group, B is most preferably an alkanediyl group. Whilst some of the hydrogen atoms of such group may be substituted by fluorine atoms, preferably B is an unsubstituted alkanediyl group, most preferably a straight chain group having 2 to 6 carbon atoms.

A particularly preferred zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

In the polymerisation process, the ethylenically unsaturated monomers may further include a comonomer. Comonomers are copolymerisable with the zwitterionic monomer and are preferably selected

from anionic, cationic and nonionic monomers. It is generally preferred that the monomer mixture include at least one nonionic monomer. Another class of comonomer is a cross-linking monomer having a functional group which may be cured after polymerisation to cross-link the polymer.

Examples of suitable comonomers are compounds of the general formula X

$$R^{31} \diagdown \underset{R^{32}}{\overset{R^{33}}{\diagup}} R^{34} \qquad X$$

in which $R^{31}$ is selected from hydrogen, halogen, $C_{1-4}$ alkyl and groups $COOR^2$ in which $R^2$ is hydrogen and $C_{1-4}$ alkyl;

$R^{32}$ is selected from hydrogen, halogen and $C_{1-4}$ alkyl;

$R^{33}$ is selected from hydrogen, halogen, $C_{1-4}$ alkyl and groups $COOR^2$ provided that $R^{31}$ and $R^{33}$ are not both $COOR^2$; and

$R^{34}$ is a $C_{1-10}$ alkyl, a $C_{1-20}$ alkoxycarbonyl, a mono-or di-$(C_{1-20}$ alkyl) amino carbonyl, a $C_{6-20}$ aryl (including alkaryl) a $C_{7-20}$ aralkyl, a $C_{6-20}$ aryloxycarbonyl, a $C_{1-20}$ -aralkyloxycarbonyl, a $C_{6-20}$ arylamino carbonyl, a $C_{7-20}$ aralkyl-amino, a hydroxyl or a $C_{2-10}$ acyloxy group, any of which may have one or more substituents selected from halogen atoms, alkoxy, oligo-alkoxy, aryloxy, acyloxy, acylamino, amine (including mono and di-alkyl amino and trialkylammonium in which the alkyl groups may be substituted), carboxyl, sulphonyl, phosphoryl, phosphino, (including mono- and di- alkyl phosphine and tri-alkylphosphonium), zwitterionic, hydroxyl groups, vinyloxycarbonyl and other vinylic or allylic substituents, and reactive silyl or silyloxy groups, such as trialkoxysilyl groups;

or $R^{34}$ and $R^{33}$ or $R^{34}$ and $R^{32}$ may together form -$CONR^{35}CO$ in which $R^{35}$ is a $C_{1-20}$ alkyl group.

It is preferred for at least two of the groups $R^{31}R^{32}$, $R^{33}$ and $R^{34}$ to be halogen or, more preferably, hydrogen atoms. Preferably $R^{31}$ and $R^{32}$ are both hydrogen atoms. It is particularly preferred that compound of general formula X be a styrene-based or acrylic based compound. In styrene based

compounds $R^{34}$ represents an aryl group, especially a substituted aryl group in which the substituent is an amino alkyl group, a carboxylate or a sulphonate group. Where the comonomer is an acrylic type compound, $R^{34}$ is an alkoxycarbonyl, an alkyl amino carbonyl, or an aryloxy carbonyl group.

5 Most preferably in such compounds $R^{34}$ is a $C_{1-20}$ -alkoxy carbonyl group, optionally having a hydroxy substituent. Acrylic compounds are generally methacrylic in which case $R^{33}$ is methyl.

Where a comonomer is included in the polymerisation process of the invention, the molar ratio of zwitterionic monomer to comonomer is

10 preferably in the range 1:50 to 50:1, more preferably in the range 1:10 to 10:1, more preferably in the range 1:5 to 1:1.

The living radical polymerisation process of the invention may be a group transfer radical polymerisation, for instance in which an N-O, or other carbon-, sulphur-, and oxygen- centered radical group is transferred from an

15 initiator compound to a monomer. Preferably, however, the process is an atom transfer radical polymerisation process.

In the atom or group transfer radical polymerisation process, the initiator has a radically transferable atom or group, and the catalyst comprises a transition metal compound and a ligand, in which the transition

20 metal compound is capable of participating in a redox cycle with the initiator and dormant polymer chain, and the ligand is either any N-, O-, P- or S-containing compound which can coordinate with the transition metal atom in a σ-bond, or any carbon-containing compound which can coordinate with the transition metal in a π-bond, such that direct bonds between the transition

25 metal and growing polymer radicals and not formed.

Preferably the radical initiator is of the general formula V

$$R^{11}R^{12}R^{13}C\text{-}X^2 \qquad\qquad V$$

where:

30 $X^2$ is selected from the group consisting of Cl, Br, I, $OR^{10}$, $SR^{14}$, $SeR^{14}$, $OP(=O)R^{14}$, $OP(=O)(OR^{14})_2$, $O\text{-}N(R^{14})_2$ and $S\text{-}C(=S)N(R^{14})_2$, where $R^{10}$ is alkyl of from 1 to 20 carbon atoms in which each of the hydrogen atoms may

be independently replaced by halide, $R^{14}$ is aryl or a straight or branched $C_1$-$C_{20}$ alkyl group, and where an $N(R^{14})_2$ group is present, the two $R^{14}$ groups may be joined to form a 5- or 6-membered heterocyclic ring; and

$R^{11}$, $R^{12}$ and $R^{13}$ are each independently selected from the group consisting of H, halogen, $C_1$-$C_{20}$ alkyl, $C_3$-$C_8$ cycloalkyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, COCl, OH, CN, $C_2$-$C_{20}$ alkenyl, $C_2$-$C_{20}$ alkenyl oxiranyl, glycidyl, aryl, heterocyclyl, aralkyl, aralkenyl, $C_1$-$C_6$ alkyl in which from 1 to all of the hydrogen atoms are replaced with halogen, $C_1$-$C_6$ alkyl substituted with from 1 to 3 substituents selected from the group consisting of $C_1$-$C_4$ alkoxy, aryl, heterocyclyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $-CR^{12}R^{13}X^2$, oxiranyl and glycidyl;

where $R^{15}$ is alkyl of from 1 to 20 carbon atoms, alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 3 carbon atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono-- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups; and

$R^{16}$ and $R^{17}$ are independently H or alkyl of from 1 to 20 carbon atoms which alkyl groups, in turn may have substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy, or $R^{16}$ and $R^{17}$ may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring;

such that not more than two of $R^{11}$, $R^{12}$ and $R^{13}$ are H.

In the initiator of the general formula V it is preferred that no more than one of $R^{11}$, $R^{12}$ and $R^{13}$, and preferably none, is hydrogen. Suitably at least one, and preferably both of $R^{11}$ and $R^{12}$ is methyl. $R^{13}$ is suitably a group CO-$R^{15}$ in which $R^{15}$ is preferably alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 3 carbon atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono-- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have

substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups.

Since any of $R^{11}$, $R^{12}$ and $R^{13}$ may comprise a substituent $C^{12}R^{13}X^2$, the initiator may be di-, oligo- or poly- functional.

5     Selection of a suitable initiator is based on various considerations. Where the polymerisation is carried out in the liquid phase, in which the monomers are dissolved, it is preferable for the initiator to be soluble in that liquid phase. The initiator is thus selected for its solubility characteristics according to the solvent system which in turn is selected according to the

10     monomers being polymerised. Also the choice of monomer will affect the polymer architecture. Star, comb, block or linear polymers may be selected by choice of a suitable initiator. A star initiator could be synthesised from a halogenated sugar. A comb initiator could be based on a polymer with pendant halogenated groups. Water-soluble initiators include, for instance

15     the reaction product of monomethoxy-capped oligo(ethylene oxide) with 2-bromoisobutyryl bromide (OEGBr), 4-bromo-α-toluic acid or ethyl 2-bromopropanoic acid or 2-(N,N-dimethylamino) ethyl-2'-bromoisobutyrate.

From the general reaction scheme shown above, it is clear that the portion of the initiator $-C-R^{11}R^{12}R^{13}$ becomes joined to the first monomer of

20     the growing polymer chain. The group $X^2$ becomes joined to the terminal unit of the polymer chain. Selection of a suitable initiator is determined in part by whether a terminal group having particular characteristics is required for subsequent functionality. Subsequent reactions of the product polymer are described below.

25     In the atom or group radical transfer polymerisation process the transition metal compound which comprises a component of the catalyst is $M_t^{n+}X'_n$, where:

$M_t^{n+}$ may be selected from the group consisting of $Cu^{1+}$, $Cu^{2+}$, $Fe^{2+}$, $Fe^{3+}$, $Ru^{2+}$, $Ru^{3+}$, $Cr^{2+}$, $Cr^{3+}$, $Mo^{2+}$, $Mo^{3+}$, $W^{2+}$, $W^{3+}$, $Mn^{2+}$, $Mn^{3+}$, $Mn^{4+}$, $Rh^{3+}$,

30     $Rh^{4+}$, $Re^{2+}$, $Re^{3+}$, $Co^+$, $Co^{2+}$, $Co^{3+}$, $V^{2+}$, $V^{3+}$, $Zn^+$, $Zn^{2+}$, $Ni^{2+}$, $Ni^{3+}$, $Au^+$, $Au^{2+}$, $Ag^+$ and $Ag^{2+}$;

X' is selected from the group consisting of halogen, $C_1$-$C_6$-alkoxy, $(SO_4)_{1/2}$, $(PO_4)_{1/3}$, $(R^{18}PO_4)\frac{1}{2}$ $(R^{18}_2PO_4)$, triflate, hexafluorophosphate, methanesulphonate, arylsulphonate, CN and $R^{19}CO_2$, where $R^{18}$ is aryl or a straight or branched $C_{1-20}$ alkyl and $R^{19}$ is H or a straight or branched $C_1$-$C_6$ alkyl group which may be substituted from 1 to 5 times with a halogen; and

n is the formal charge on the metal ($0 \leq n \leq 7$).

Preferably X' is halide, most preferably chloride or bromide.

Particularly suitable transition metal compounds are based on copper or ruthenium, for instance CuCl or $RuCl_2$.

In the catalyst, the ligand is preferably selected from the group consisting of:

a)     compounds of the formulas:

$$R^{20}\text{-}Z\text{-}R^{21} \quad \text{and}$$

$$R^{20}\text{-}Z\text{-}(R^{22}\text{-}Z)_m\text{-}R^{21}$$

where:

$R^{20}$ and $R^{21}$ are independently selected from the group consisting of H, $C_1$-$C_{20}$ alkyl, aryl, heterocyclyl and $C_1$-$C_6$ alkoxy, $C_1$-$C_4$ dialkylamino, $C(=O)R^{22}$, $C(=O)R^{23}R^{24}$ and $A^7C(=O)R^{25}$, where $A^7$ may be $NR^{26}$ or O; $R^{22}$ is alkyl of from 1 to 20 carbon atoms, aryloxy or heterocyclyloxy; $R^{23}$ and $R^{24}$ are independently H or alkyl of from 1 to 20 carbon atoms or $R^{23}$ and $R^{24}$ may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring; $R^{25}$ is H, straight or branched $C_1$-$C_{20}$ alkyl or aryl and $R^{26}$ is hydrogen, straight or branched; $C_{1-20}$-alkyl or aryl; or $R^{20}$ and $R^{21}$ may be joined to form, together with Z, a saturated or unsaturated ring;

Z is O, S, $NR^{27}$ or $PR^{27}$, where $R^{27}$ is selected from the same group as $R^{20}$ and $R^{21}$, and where Z is $PR^{27}$, $R^{27}$ can also $C_1$-$C_{20}$ alkoxy or Z may be a bond, $CH_2$ or a fused ring, where one or both of $R^{20}$ and $R^{21}$ is heterocyclyl,

each $R^{22}$ is independently a divalent group selected from the group consisting of $C_1$-$C_8$ cycloalkanediyl, $C_1$-$C_8$ cycloalkenediyl, arenediyl and

heterocyclylene where the covalent bonds to each Z are at vicinal positions
or $R^{22}$ may be joined to one or both of $R^{20}$ and $R^{21}$ to formulate a heterocyclic
ring system; and

m is from 1 to 6;

5      b)    CO;

c)    porphyrins and porphycenes, which may be substituted with
from 1 to 6 halogen atoms, $C_{1-6}$ alkyl groups, $C_{1-6}$-alkoxy groups, $C_{1-6}$
alkoxycarbonyl, aryl groups, heterocyclyl groups, and $C_{1-6}$ alkyl groups
further substituted with from 1 to 3 halogens;

10      d)    compounds of the formula $R^{23}R^{24}C(C(=O)R^{25})_2$, where $R^{25}$ is $C_{1-20}$
alkyl, $C_{1-20}$ alkoxy, aryloxy or heterocyclyloxy; and each of $R^{23}$ and $R^{24}$ is
independently selected from the group consisting of H, halogen, $C_{1-20}$ alkyl,
aryl and heterocyclyl, and $R^{23}$ and $R^{24}$ may be joined to form a $C_{1-8}$ cycloalkyl
ring or a hydrogenated aromatic or heterocyclic ring, of which the ring atoms
15    may be further substituted with 1 to 5 $C_{1-6}$ alkyl groups, $C_{1-6}$ alkoxy groups,
halogen atoms, aryl groups, or combinations thereof; and

e)    arenes and cyclopentadienyl ligands, where said
cyclopentadienyl ligand may be substituted with from one to five methyl
groups, or may be linked through and ethylene or propylene chain to a
20    second cyclopentadienyl ligand.

Selection of a suitable ligand is, for instance, based upon the
solubility characteristics and/or the separability of the catalyst from the
product polymer mixture. Generally it is catalyst to be soluble in a liquid
reaction mixture, although under some circumstances it may be possible to
25    immobilise the catalyst, for instance an a porous substrate. For the
preferred process, which is carried out in the liquid phase, the ligand is
soluble in a liquid phase. The ligand is generally a nitrogen containing
ligand. The preferred ligand may be a compound including a pyridyl group
and an imino moiety, such as bipyridine, or

30
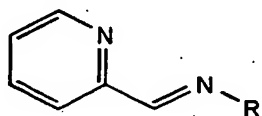
where R is a suitable alkyl group, the substituent being variable and adaptable to confer desired solubility characteristics or may be triphenylphosphine or 1,1,4,7,10,10-hexamethyl-triethylene tetramine.

Such ligands are usefully used in combination with copper chloride
5    and ruthenium chloride transition metal compounds as part of the catalyst.

The living radical polymerisation process of the invention is preferably carried out to achieve a degree of polymerisation in the range 5 to 500. Preferably the degree of polymerisation is in the range 10 to 100, more preferably in the range 10 to 50. In the preferred group or atom transfer
10   radical polymerisation technique, the degree of polymerisation is directly related to the initial ratios of initiator to monomer. Preferably the ratio is in the range 1:(5 to 500), more preferably in the range of 1:(10 to 100), most preferably in the range 1:(10 to 50).

The ratio of metal compound and ligand in the catalyst should be
15   approximately stoichiometric, based on the ratios of the components when the metal ion is fully complexed. The ratio should preferably be in the range 1:(0.5 to 2) more preferably in the range 1:(0.8:1.25). Preferably the range is about 1:1.

In the process, the catalyst may be used in amounts such that a molar
20   equivalent quantity as compared to the level of initiator is present. However, since catalyst is not consumed in the reaction, it is generally not essential to include levels of catalyst as high as of initiator. The ratio of catalyst (based on transition metal compound) to initiator is preferably in the range 1:(1 to 50), more preferably in the range 1:(1 to 10).

25   Whilst the polymerisation reaction may be carried out in the gaseous phase, it is more preferably carried out in the liquid phase. The reaction may be heterogeneous, that is comprising a solid and a liquid phase, but is more preferably homogeneous. Preferably the polymerisation is carried out in a single liquid phase. Where the monomer is liquid, it is sometimes
30   unnecessary to include a non-polymerisable solvent. More often, however, the polymerisation takes place in the presence of a non-polymerisable solvent. The solvent should be selected having regard to the nature of the

zwitterionic monomer and any comonomer, for instance for its suitability for providing a common solution containing both monomers. The solvent may comprise a single compound or a mixture of compounds.

It has been found that, especially where the zwitterionic monomer is

5 MPC, that it is desirable to include water in the polymerisation mixture. Preferably water should be present in an amount in the range 10 to 100% by weight based on the weight of ethylenically unsaturated monomer. Preferably the total non-polymerisable solvent comprised 1 to 500% by weight based on the weight of ethylenically unsaturated monomer. It has

10 been found that the zwitterionic monomer and water should be in contact with each other for as short a period as possible prior to contact with the initiator and catalyst. It may be desirable therefore for all the components of the polymerisation other than the zwitterionic monomer to be premixed and for the zwitterionic monomer to be added to the premix as the last additive.

15 It is often desired to copolymerise MPC or other zwitterionic monomer with a comonomer which is insoluble in water. In such circumstances, a solvent or co-solvent (in conjunction with water) is included to confer solubility on both MPC and the more hydrophobic monomer. Suitable organic solvents are ethers, esters and, most preferably, alcohols.

20 Especially where a mixture of organic solvent and water is to used, suitable alcohols are $C_{1-4}$ -alkanols. Methanol is found to be particularly suitable in the polymerisation process of the invention.

The process may be carried out at raised temperature, for instance up to 60 to 80 °C. However it has been found that the process proceeds

25 sufficiently fast at ambient temperature.

The polymerisation process of the invention has been found to provide polymers of zwitterionic monomers having a polydispersity (of molecular weight) of less than 1.5, as judged by gel permeation chromatography. Polydispersities in the range 1.2 to 1.4 have been

30 achieved. Conversion rates achieved in the process are over 90% often over 95% or higher. It is preferred that the process be continued until a conversion level of at least 50%, or usually, at least 70% is reached.

It is believed that this process is the first time that low polydispersity polymers have been formed of monomers of the general formula I and such polymers form a further aspect of the invention.

Such polymers are preferably made by the living radical polymerisation process of the first aspect of the invention. Other controlled polymerisation techniques may be used for instance NO group transfer systems such as are described in WO-A-0018807, catalyst systems described in WO-A-9958588, systems involving irradiation with visible light, or other EM radiation such as described in WO-A-99/10387, radical addition fragmentation chain transfer polymerisation (RAFT) as described in Rizzardo, E. *et al.* ACS Symposium Series 2000, 768, 278-296, using compounds (initiators) of the general type Z-C=SSR or macromolecular design through interchange of xanthes (MADIX) as descried by Bontevin, B., J. Polym.Sci. PtA, Polym.Chem., 2000, 38(18), 3235-3243.

The polymer product of the polymerisation process of the invention may be a useful product as such. It may be desirable to deactivate or functionalise the terminal groups, that is the $CR^{11}R^{12}R^{13}$ and/or $X^2$ groups. The presence of such groups in the final polymer may provide useful functionality for subsequent chemical reactions. For instance tertiary amine substituents in such groups may be quaternised, ethylenic groups may be polymerised, and crosslinkable groups may be cured.

The product polymer may be a useful intermediate for forming block copolymers. A product polymer having a single terminal group $X^2$ may be used as an initiator in a second group or atom transfer radical polymerisation step carried out in the presence of a catalyst, and additional ethylenically unsaturated monomer. The product will be a block copolymer of the A-B type. The second block may be of the same or, more usefully, a different composition to that of the initial block A. The monomers from which block A and block B are formed may comprise the same component but in different ratios. More often they comprise different monomers, although they may include common comonomers. A second block, for instance added to a block A formed from zwitterionic monomer, may comprise ionic monomer or

nonionic monomer. Nonionic monomer may be selected so as to confer hydrophobicity or control the hydrophilicity of the block copolymer. Suitable monomers used in a second living polymerisation step may include monomers of the general formula V, defined above. Comonomers may be

5      selected to confer biodegradability upon the block copolymers.

A block copolymer of the A-B-A type may be produced where the initiator of a first step living polymerisation was difunctional, generating a single block B having two terminal groups $X^2$ (and a unit derived from the initiator partway along the backbone). In the second living polymerisation

10     step, blocks of A will be added at each end of the initial polymer product. Alternatively, block copolymers having a star type architecture may be generated starting from a multifunctional initiator in the first step producing a star intermediate having, at each terminal, a $X^2$ group, from which the second step polymerisation propagates.

15     According to a second aspect of the invention there is provided a block copolymer of the A-B or A-B-A type in which A and B are the same or, preferably, different, in which at least one of the A and B is formed from ethylenically unsaturated monomer including a zwitterionic monomer of the general formula VI

20                            Y B X$^1$                              VI

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,

25
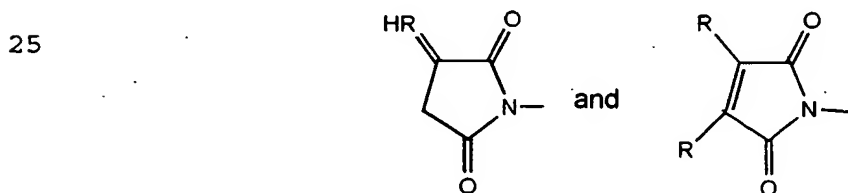


A is -O- or $NR^1$;

30     $A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n SO_3-$ in which n is 1 to 12;

$A^2$ is selected from a bond -O-, O-CO-, CO-O, CO-NR$^1$-, -NR$^1$-CO, O-CO-NR$^1$-, NR$^1$-CO-O-;

R is hydrogen or $C_{1-4}$ alkyl;

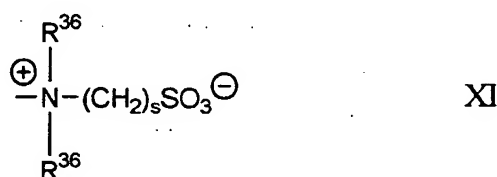R$^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

5       R$^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

X$^1$ is a zwitterionic group.

10      In this aspect of the invention, the zwitterionic group X$^1$ may be a group X as defined in the first aspect of the invention. Alternatively it may be a zwitterion in which the anion comprises a sulphate, sulphonate or carboxylate group.

One class of zwitterions are sulphobetaines groups, for instance of

15      the general formula XI.

$$\overset{\displaystyle R^{36}}{\underset{\displaystyle R^{36}}{\overset{\displaystyle |}{\underset{\displaystyle |}{-\overset{\oplus}{N}-(CH_2)_s SO_3^{\ominus}}}}} \qquad XI$$

20      where the groups R$^{36}$ are the same or different and each is hydrogen or $C_{1-4}$ alkyl and s is from 2 to 4.

Preferably the groups R$^{36}$ are the same. It is also preferable that at least one of the groups R$^{36}$ is methyl, and more preferable that the groups R$^{36}$ are both methyl.

25      Preferably s is 2 or 3, more preferably 3.

Alternatively the zwitterionic group may be an amino acid moiety in which the alpha carbon atom (to which an amine group and the carboxylic acid group are attached) is joined through a linker group to the backbone of the biocompatible polymer. Such groups may be represented by the general

30      formula XII
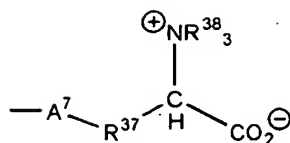
$$-A^7 \underset{R^{37}}{\overset{\overset{\displaystyle \oplus NR^{38}_3}{|}}{\underset{H}{\overset{|}{C}}}} CO_2^{\ominus} \qquad \text{XII}$$

5　　　　　in which $A^7$ is a valence bond, -O-, -S- or -NH-, preferably -O-,

$R^{37}$ is a valence bond (optionally together with $A^7$) or alkanediyl, -C(O)alkylene- or -C(O)NHalkylene, preferably alkanediyl and preferably containing from 1 to 6 carbon atoms; and

the groups $R^{38}$ are the same or different and each is hydrogen or alkyl

10　　　　of 1 to 4 carbon atoms, preferably methyl, or two or three of the groups $R^{38}$, together with the nitrogen to which they are attached, form a heterocyclic ring of from 5 to 7 atoms, or the three group $R^{38}$ together with the nitrogen atom to which they are attached form a fused ring heterocyclic structure containing from 5 to 7 atoms in each ring.
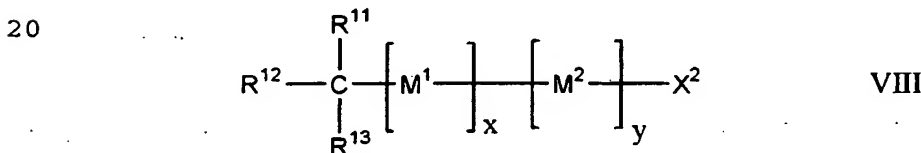
15　　　　Alternatively the zwitterion may be a carboxy betaine - $N^{\oplus}(R^{39})_2(CH_2)_rCOO^{\ominus}$ in which the $R^{39}$ groups are the same or different and each is hydrogen or $R_{1-4}$ alkyl and r is 2 to 6, preferably 2 or 3.

In this aspect of the invention it may either be the first formed block which comprises zwitterionic monomer, or the second formed block. It is

20　　　　preferred that either or both blocks are formed by living polymerisation techniques, that is that the population of polymers should have a low spread of block sizes, and of overall polydispersity of weight. Preferably both blocks are formed by atom or group transfer radical polymerisation. At least one of the steps of a two step process is that a polymerisation process according to

25　　　　the first aspect of the invention, namely the step in which the ethylenically unsaturated monomers include zwitterionic monomer. In a two step polymerisation both being carried out by atoms or group radical transfer, the group or atom transferred, as the case may be, will be the same in the two step. The transferable group which is the terminal group of the polymer

30　　　　product of the first step is transferred to a transition metal compound in the initiation of the second step. Generally it is convenient to use the same catalyst. In some circumstances, however, it may be necessary to use a

different catalyst, for instance a different transition metal compound or ligand, or both, if the environment in the second step of the polymerisation is very different from that of the first step. For instance where the monomers in the second step require selection of a different solvent to solubilise the

5    components, a different catalyst may be selected. Accordingly it may be necessary to isolate the polymer intermediate of step one from the catalyst, prior to providing the reaction mixture for step two. Suitable separation methods involve, for instance, chromatographic techniques such as gel permeation or precipitation etc. Preferably, however, the product of step one, in its entirety, forms part of the reaction mixture for step two.

10

The intermediate polymer produced by the process of the first aspect of the invention may be a useful commercial product in its own right, for instance having utility as an initiator for group or atom transfer radical polymerisations. Alternatively the terminating groups derived from the

15    initiator may be subjected to derivatisation reactions to introduce useful functionalities such as ionic groups and/or ethylenically unsaturated groups.

According to a further aspect of the invention there is provided a novel polymer of the formula VIII

20

$$R^{12}\!\!-\!\!\underset{\underset{R^{13}}{\overset{\overset{R^{11}}{|}}{\underset{|}{C}}}{}\!\!-\!\!\left[M^1\!-\!\right]_x\!\!-\!\!\left[M^2\!-\!\right]_y\!\!-\!X^2 \qquad \text{VIII}$$

in which $X^2$ is selected from the group consisting of Cl, Br, I, $OR^{10}$, $SR^{14}$,

25    $SeR^{14}$, $OP(=O)R^{14}$, $OP(=O)(OR^{14})_2$, $O\text{-}N(R^{14})_2$ and $S\text{-}C(=S)N(R^{14})_2$, where $R^{10}$ is alkyl of from 1 to 20 carbon atoms in which each of the hydrogen atoms may be independently replaced by halide, $R^{14}$ is aryl or a straight or branched $C_1\text{-}C_{20}$ alkyl group, and where an $N(R^{14})_2$ group is present, the two $R^{14}$ groups may be joined to form a 5- or 6-membered heterocyclic ring; and

30    $R^{11}$, $R^{12}$ and $R^{13}$ are each independently selected from the group consisting of H, halogen, $C_1\text{-}C_{20}$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, COCl, OH, CN, $C_2\text{-}C_{20}$ alkenyl, $C_2\text{-}C_{20}$ alkenyl oxiranyl,

glycidyl, aryl, heterocyclyl, aralkyl, aralkenyl, $C_1$-$C_6$ alkyl in which from 1 to all of the hydrogen atoms are replaced with halogen, and $C_1$-$C_6$ alkyl substituted with from 1 to 3 substituents selected from the group consisting of $C_1$-$C_4$ alkoxy, aryl, heterocyclyl, $C(=O)R^{15}$, $C(=R)NR^{16}R^{17}$, $-CR^{12}R^{13}X^2$, oxiranyl and glycidyl;

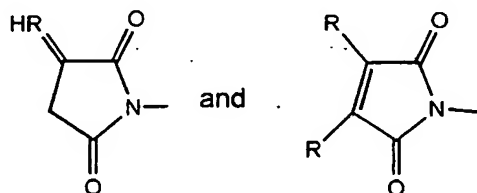where $R^{15}$ is alkyl of from 1 to 20 carbon atoms, alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 5 carbon atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups; and $R^{16}$ and $R^{17}$ are independently H or alkyl of from 1 to 20 carbon atoms which alkyl groups, in turn may have substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy, or $R^{16}$ and $R^{17}$ may be joined together to form an alkylene group of from 2 to 5 carbon atoms, thus forming a 3- to 6- membered ring;

such that not more than two of $R^{11}$, $R^{12}$ and $R^{13}$ are H;

$M^1$ is the residue of a zwitterionic monomer zwitterionic monomer of the general formula I

$$Y \ B \ X \qquad I$$

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,



A is -O- or $NR^1$;

$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n$ $SO_3$- in which n is 1 to 12;

$A^2$ is selected from a bond -O-, O-CO-, CO-O, CO-NR$^1$-, -NR$^1$-CO, O-CO-NR$^1$-, NR$^1$-CO-O-;

R is hydrogen or $C_{1-4}$ alkyl;

R$^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

5　　　　R$^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;
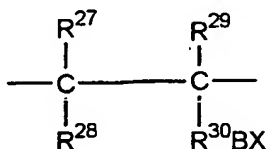
X is an ammonium, phosphonium, or sulphonium phosphate or

10　　phosphonate ester zwitterionic group;

x is 2 to 500;

$M^2$ is the residue of an ethylenically unsaturated comonomer polymerisable with the zwitterionic monomer; and

y is 0 to 500.

15　　　　In a preferred polymer of this aspect in the general formula VIII M$^1$ preferably has the formula IX

$$\underset{\overset{|}{R^{28}}}{\overset{\overset{R^{27}}{|}}{-C}}-\underset{\overset{|}{R^{30}BX}}{\overset{\overset{R^{29}}{|}}{C}}-\qquad\qquad IX$$

20

in which R$^{27}$ is selected from hydrogen $C_{1-4}$ alkyl and groups CO OR$^2$ in which R$^2$ is hydrogen or $C_{1-4}$ alkyl;

R$^{28}$ is selected from hydrogen and $C_{1-4}$ alkyl;

R$^{29}$ is selected from hydrogen, $C_{1-4}$ alkyl and groups CO OR$^2$,

25.　　provided that R$^{27}$ and R$^{29}$ are not both CO OR$^2$;

R$^{30}$ is selected from a bond, a group CH$_2$A$^2$ in which A$^2$ is selected from a bond, -O-, -O-CO-, -CO-O-, -CO-NR$^1$-, -NR$^1$-CO-, -O-CO-NR$^1$- and -NR$^1$-CO-O, a group -COA- in which A is -O- or NR$^1$, in which R$^1$ is hydrogen or $C_{1-4}$ alkyl or BX, and a group -C$_6$H$_4$-A$^1$- in which A$^1$ is (CH$_2$)$_n$A$^2$, a bond or

30　　(CH$_2$)$_n$SO$_3$,

or R$^{30}$ and R$^{28}$ or R$^{30}$ and R$^{21}$ may be joined to form a group

$$-CO-\overset{|}{N}-CO-$$

where the N atom is joined to B;

and B and X are as defined above.

In the polymer of the general formula VIII, $M^2$ is preferably the residue of a monomer of the general formula X as described above. The group $M^2$, derived from such a monomer will have the general formula

$-C(R^{31})(R^{32}-C(R^{33})R^{34})$, in which $R^{31}$ through $R^{34}$ have the same meanings as in the general formula X.

In the polymer of the general formula X, $R^{11}$, $R^{12}$ and $R^{13}$ as well $X^2$ have the preferred meanings ascribed to the respective groups in the initiator described in relation to the first aspect of the invention above. Thus $X^2$ is preferably halogen, more preferably Cl or Br. Preferably no more than one of $R^{11}$, $R^{12}$ and $R^{13}$ is hydrogen, more preferably none is hydrogen.

In the general formula VIII the residues of $M^2$ are randomly dispersed among the residues of $M^1$.

In the invention, the controlled molecular weight, composition and architectures of these various product polymers bring about desirable levels of control in the properties of the polymers. For instance, the provision of blocks of substantially homopolymer of units derived from zwitterionic monomer are believed to confer desirable wettability and/or lubricity. In AB block copolymers or polymers formed using oligomeric initiators such as based on oligo(alkylene oxides), the provision of long blocks of hydrophobic units are likely to form discrete domains. The domains of highly hydrophilic and highly hydrophobic composition may be useful for controlling polymer properties, such as interactions with other components in a desired system, especially for the absorption and controlled delivery of drugs or other active compounds, and for providing spontaneously self-assembling structures such as coatings, or vesicles or micelles having domains of hydrophilic and domains of hydrophobic nature. These may be useful for controlling absorption and release or solubility of biologically active compounds such as

pharmaceuticals. Vesicles may form, with dehydrated or hydrophobic layers or cores and zwitterionic exteriors in aqueous environments. The external zwitterionic layer should confer good biocompatibility, for instance resistance to phagocytosis when administered *in vivo*. This may be a useful drug delivery device, therefore.

The invention is illustrated further in the accompanying examples, and figures.

Figures 1 and 2 are plots of the reaction kinetics of Example 1;

Figure 3 is the $^1$H NMR spectrum of the polymer produced in Example 1;

Figures 4 and 5 are plots of the reaction kinetics of Example 3;

Figures 6 and 7 are $^1$H NMR spectra of the block copolymer produced in Example 4 and pH9 and 3, respectively;

Figure 8 is a $^1$H NMR spectrum of the block copolymer produced in Example 24 at two pH's as described in Example 30;

Figure 9 shows the $^1$H NMR spectrum and chemical formulae for the initiator, monomer and polymer of Example 31;

Figure 10 shows the $^1$H NMR during the polymerisation process of Example 31;

Figure 11 indicates drug loading levels in Example 58; and

Figure 12 indicates drug release levels in Example 58.

**Example 1: Homopolymerisation of MPC (1) *via* ATRP in Water.**

With reference to Figure 1, a typical protocol for the controlled polymerisation of 1 by aqueous ATRP is as follows. A water-soluble ATRP initiator (OEGBr, 413 mg, 0.67 mmol, 1 equiv.) was synthesised as reported previously E. J. Ashford, V. Naldi, R. O'Dell, N. C. Billingham and S. P. Armes, *Chem. Commun.*, 1285, 1999 and dissolved in doubly-distilled, de-ionised water (10 ml). After purging with nitrogen for 30 min. Cu(I)Br catalyst (96 mg, 0.67 mmol, 1 equiv.) and bipyridine (bpy) ligand (208 mg, 0.13 mmol, 2 equiv.) were added to the stirred solution under a flow of nitrogen. Monomer 1 (2 g, 6.7 mmol, 10 equiv.) was then added as a solid to the

reaction mixture under nitrogen. The reaction mixture immediately became

dark green and progressively more viscous. Exotherms of 2-4 °C were

typically observed, indicating that polymerisation was occurring. After the

reaction was complete the resulting homopolymer 1 was precipitated from

5    THF, then redissolved in water and passed through a silica column to remove

residual ATRP catalyst.

Further polymerisations were conducted at different concentrations

and ratios of monomer and initiator. In all cases the ATRP of 1 in water was

rapid: exotherms of around 3 °C were observed and near-quantitative yields

10   (> 96 %) were obtained within 10 minutes at 20 °C and 17 wt.% monomer

concentration. At higher monomer concentration (40 wt.%) yields of more

than 96 % were obtained within 3 minutes. However, polydispersities were a

little higher at 1.23 – 1.45, indicating some loss of control under these

conditions.

15   The semi-logarithmic kinetic plot for the homopolymerisation of 1

Conditions: [monomer] = 17 wt. %, [initiator] = 24 mM; pH 7; the molar ratio of

monomer: initiator: copper(I): bpy was 28: 1: 1: 2, 20°C.) is linear for the first

50 % of the polymerisation (see Figure 1). At higher conversions non-linear

behaviour is observed, indicating that the polymer radical concentration is no

20   longer constant. On the other hand, the evolution of molecular weight with

conversion is highly linear up to 95 % conversion (see Figure 2).

Molecular weight distributions were assessed using GPC (1.0 M NaCl

solution with 50 mM Trisma buffer, Superdex 200 column, PEO standards, RI

detector). The kinetics of polymerisation were monitored by $^1$H NMR

25   spectroscopy by comparing the peak integrals due to the monomer vinyl

signals (at δ 5.5 and 5.9) to those of the methacrylate backbone (at δ 0.5 to

1.1) (see Figure 3).

GPC analysis indicates narrow, unimodal molecular weight

distributions, with polydispersities (Mw/Mn) of around 1.1 to 1.45 (see Table

30   1). The initiator was used as an 'end-group' to determine the degrees of

polymerisation of the homopolymers by $^1$H NMR spectroscopy (see Table 1).

In these calculations it is assumed that the initiator efficiency is 100 %, chain

transfer is negligible and that every polymer chain contains an oligo(ethylene glycol) fragment. The latter assumption was confirmed by the following experiment. An aqueous solution of poly1 (degree of polymerisation = 20) was precipitated into THF, which is a good solvent for the oligo(ethylene glycol)-based initiator. No change in the degree of polymerisation of the precipitated homopolymer was detected by NMR, which confirmed that all of the initiator groups were covalently attached to the polymer chains, as expected. For this example only relatively low degrees of polymerisation were targeted, partly because of the known exclusion limits of our GPC column.

**Example 2: Homopolymerisation of MPC *via* ATRP in Methanol.**

The feasibility of polymerising **1** in methanol at 20 °C was also investigated. Well-controlled ATRP occurred much more slowly under these conditions, with conversions of only 70 % after 4h. Aqueous GPC analysis indicated a final polydispersity of 1.12 at a monomer concentration of 17 wt. %. However, ATRP in aqueous media is preferred since very high yields are achieved much more efficiently (Table 1).

27

Table 1: Summary of synthesis conditions, molecular weight data and conversions for the homopolymerisation of the phosphorylcholine-based monomer (1) via ATRP at 20 °C in either water or methanol.

| Solvent | [Monomer] (wt. %) | [Initiator] (mM) | TheoreticalDp | Experimental Dp[a] | Experimental $M_n$[b] | $M_w/M_n$[b] | Conversion (%) |
|---|---|---|---|---|---|---|---|
| $H_2O$ | 17 | 0 | c | c | c | c | 53[c] |
| $H_2O$ | 17 | 67 | 10 | 11 | 4,710 | 1.18 | >96 |
| $H_2O$ | 17 | 40 | 17 | 18 | 6,900 | 1.28 | >96 |
| $H_2O$ | 40 | 222 | 10 | 10 | 4,230 | 1.23 | >96 |
| $H_2O$ | 40 | 111 | 20 | 20 | 7,550 | 1.39 | >96 |
| $H_2O$ | 40 | 73 | 30 | 29 | 10,720 | 1.45 | >96 |
| MeOH | 17 | 67 | 10 | 11 | 3,800 | 1.12 | >96 |
| MeOH | 40 | 73 | 30 | 29 | 8,640 | 1.41 | >96 |

[a] From ^{1}H NMR spectroscopy (see text for details).

[b] From aqueous GPC analysis.

[c] This was a spontaneous polymerisation with no initiator, therefore a theoretical Dp could not be calculated. The conversion stated was measured at 5h. Aqueous GPC column limits were exceeded, rendering quantitative analysis meaningless.

### Example 3: Homopolymerization of MPC in $H_2O$ via ATRP using methanol as a co-solvent.

A two-neck round-bottom 100 ml flask was charged with OEG-Br, CuCl and bipy. Water (8.0 ml) was added and the mixture was stirred until a homogeneous solution was obtained. Monomer 1 (2.0 g) was dissolved in degassed methanol (2.0 ml), added to the reaction solution and the flask was sealed with a rubber septum. The reaction mixture was maintained under dry nitrogen for the duration of the polymerisation. The molar ratio of [1]:[CuCl]:[bipy]:[initiator] used in this case was 20:1:2:1, i.e. the target Dp was 20.

A plot of $\ln([M]_0/[M])$ against time homopolymerisation of HEMA-PC at 20°C. $[HEMA-PC]_0 = 0.67$ M; $[OEG_{350}-Br]_0 = 0.033$ M; $[CuCl]_0 = 0.033$ M; $[bipy]_0 = 0.066$M; $H_2O = 8.0$ ml, MeOH = 2.0 ml was linear and passed through the origin, demonstrating that the radical concentration remained constant on the time-scale of the polymerisation, see Figure 4. The experimental $M_n$ values obtained from $^1H$ NMR agreed well with the theoretical line, see Figure 5 (same conditions). Polydispersities remained low throughout the polymerisation (Mw/Mn ≤1.3) which is indicative of a living polymerisation. In summary, methanol can be used as a co-solvent for 1 which enables this monomer to be conveniently handled as a solution, rather than as a solid. If the methanol content is relatively low (in this case 20 vol %) there appears to be no detrimental effect on the rate of polymerisation.

Table 2: Kinetic data for the homopolymerisation of HEMA-PC via ATRP in 20:80 methanol/water mixture at 20 °C. The conditions were: [HEMA-PC] = 0.67 M, [OEG-Br] = 0.033 M, [CuCl] = 0.033 M, [bipy] = 0.066 M, $H_2O$ = 8.0 ml, MeOH = 2.0 ml.

| No. | Time ( min. ) | Conv ( % ) | Mn ( theory ) | Mn ( NMR ) | Mw / Mn |
|-----|-----|-----|-----|-----|-----|
| 1 | 0.5 | 4 | 259 | 291 | 1.14 |
| 2 | 1 | 8 | 466 | 437 | 1.17 |
| 3 | 2 | 13 | 768 | 728 | 1.19 |
| 4 | 5 | 35 | 2060 | 1770 | 1.21 |
| 5 | 10 | 61 | 3590 | 3160 | 1.22 |
| 6 | 20 | 86 | 5070 | 4410 | 1.26 |
| 7 | 35 | 99 | 5810 | 5180 | 1.31 |

**Example 4: AB-Diblock MPC-NaVBA Copolymer Formation *via* ATRP.**

Diblock copolymers based on 1 can also be synthesised *via* aqueous ATRP. For example, sodium 4-vinylbenzoate (NaVBA) (0.5 g, 3.4 mmol) was homopolymerised ([NaVBA]=13 wt.%, [I]=20 mM, $D_p$=46) to high yield (> 90 %) in water (3.5 ml) at pH 11 and 20 °C using OEGBr as initiator, as described previously X. S. Wang, R. A. Jackson and S. P. Armes, *Macromolecules*, 2000, **33**, 255.[13] At this point monomer 1 (1.0 g, 3.4 mmol) was added as a solid to this reaction solution ([1]=22 wt.%, [I]=20 mM, theoretical $D_p$=46) to form a diblock copolymer.

^{1}H NMR studies indicated that the block copolymer comprised approximately 55 mol % NaVBA, theoretical $D_p$(NaVBA)=46, $D_p$(1)=37, see Figure 6. This block copolymer dissolved molecularly in water at pH 7 but formed micellar aggregates reversibly on addition of acid (pH 3), see Figure 7. Dynamic light scattering studies indicated a bimodal size distribution, with the larger population having an intensity-average micelle diameter of 190 nm. ^{1}H NMR studies of these micelles in $DCl/D_2O$ mixtures confirmed that the 4-vinylbenzoic acid residues formed the dehydrated micelle cores and the phosphorylcholine-based residues formed the micelle coronas, as expected. Such micelles might be expected to act as 'stealth' nanoparticles for *in vivo* biomedical applications, since the phosphorylcholine outer layer should

minimise protein adsorption and hence prevent phagocytosis.


### Example 5:  AB-Diblock MPC-HEMA Copolymer Formation *via* ATRP.

1 (2.0 g, 6.7 mmol) was polymerised in water (10 ml) as described for
the homopolymerisation ([1]=17 wt.%, [I]=34 mM, theoretical $D_p$=20), but after
12 min (98% conversion) a degassed solution of HEMA (2-hydroxyethyl
methacrylate) (0.88 g, 6.7 mmol) in methanol (5 ml) was added to give a
reaction solution composition of 67:33 water:methanol ([HEMA]=6 wt.%,
[I]=23 mM, theoretical $D_p$=20). 1 h after the addition of the second monomer
the overall conversion for the polymerisation had reached over 98%. The
actual degree of polymerisation was 19 for each block ((1), HEMA) as judged
by $^1$H NMR spectroscopy.


### Example 6:  AB-Diblock MPC-HEMA Copolymer Formation *via* ATRP Directly in a H$_2$O:MeOH Solvent Mixture.

Block copolymerisation of 1 with HEMA. 1 (4.1 g, 1.35×10$^{-2}$ mol) was
polymerised first in 10.0 ml of a 50/50 vol/vol methanol/water mixture such that
the molar ratios of [1]:[OEG-Br]:[CuCl]:[bipy] were 10:1:1:2. After 150 min, the
monomer conversion was 100 %, and the homopolymer obtained had a low
polydispersity (Mw / Mn = 1.19) with an Mn of 3,000. HEMA (3.54 g, 2.7×10$^{-2}$
mol, target Dp = 20), was then added to the polymerising aqueous solution.
After 24 h, a diblock copolymer was obtained with essentially 100 % monomer
conversion. The copolymer Mn was calculated by end-group analysis using $^1$H
NMR. GPC analysis was not possible in this case because the copolymer
formed micelles in water.


### Example 7:  AB-Diblock MPC-OEGMA Copolymer Formation *via* ATRP.

Another block copolymer was prepared in a similar fashion to Example
4, first 1 (2.0 g, 6.7 mmol) was polymerized in water (10 ml) as described
previously ([1]=17 wt.%, [I]=34 mM, theoretical $D_p$=20) and at 11 min (97%
conversion) a degassed solution of OEGMA (oligoethylene glycol methacrylate)

31

(2.87 g, 6.7 mmol) in water (2 ml) was added ([OEGMA]=19 wt.%, [I]=28 mM, theoretical $D_p$=20). 20 min after the addition of the second monomer $^1$H NMR spectroscopy was used to calculate an overall conversion of more than 98% for the diblock copolymer and a degree of polymerisation of 20 for each block. Aqueous GPC analysis gave an $M_n$ of 8,750 and an $M_w/M_n$ of 1.30 for homopolymer (1) and an $M_n$ of 12,900 and an $M_w/M_n$ of 1.34 for the diblock.

**Example 8: AB-Diblock OEGMA-MPC Copolymer Formation *via* ATRP.**

OEGMA (5.03 g, $1.2 \times 10^{-2}$ mol) was polymerised first in water (10 ml) under the following conditions: [OEGMA]:[OEG-Br]:[CuCl]:[bipy] = 20:1:1:2; target Dp = 20. After 20 min, the monomer conversion reached 100 % with Mn = 8,600 and Mw/Mn = 1.19, as judged by aqueous GPC. 1 was then added as a solid (3.56 g, $1.2 \times 10^{-2}$ mol; target Dp = 20) to the polymerising OEGMA solution. Essentially 100 % monomer conversion was achieved after 60 min, as indicated by $^1$H NMR spectroscopy (no residual vinyl double bonds). After clean-up and isolation, a diblock copolymer (Mn = 15,000) was obtained with a relatively low polydispersity (Mw/Mn ~ 1.4).

**Example 9: AB-Diblock MPC-DMAPS Copolymer Formation *via* ATRP.**

1 can also be block copolymerised with DMAPS ([2-(Methacryloyloxy) ethyl] dimethyl (3-sulfopropyl) ammonium hydroxide). 1 (4.0 g, $1.35 \times 10^{-2}$ mol) was homopolymerised first in water (10 ml); [1]:[OEG-Br]:[CuCl]:[bipy} = 20:1:1:2, target Dp = 20. After 120 min, the monomer conversion was 100%, and the homopolymer obtained (Mn = 6,200) had a low polydispersity (Mw / Mn = 1.20). DMAPS monomer (3.8 g, $1.35 \times 10^{-2}$ mol, target Dp = 20) was then added to the polymerising aqueous solution. After 21 h, a block copolymer with an Mn of 12,000 and a polydispersity of 1.27 was obtained.

**Examples 10-15: AB-diblock Copolymer Formulation with other Comonomers**

MPC was further polymerised using the general technique for AB block copolymers with the conditions indicated in Table 5 and with monomers of

varying hydrophobicity. The comonomer type, proportion and intended degree of polymerisation is shown in the table. The extent of conversion after the specified reaction time as well as the measured number average molecular weight (by NMR) are also shown in the table.

**Table 3 - Synthesis of MPC based diblock copolymers via statistical polymerisation**

ATRP [MPC] = 0.67M, [OEG-Br] = 0.067M, [CuBr] = 0.067M, [bipy] = 0.135M, MeOH = 10ml, T = 20°C

| Example # | Comonomer | MPC in copolymer (mol%) | Target Dp | Time ( h ) | Conversion (%) | Mn (cal) | Mn (NMR) |
|---|---|---|---|---|---|---|---|
| 10 | HEMA | 10 | 10:90 | 6 | >99 | 15000 | 13000 |
| 11 | nBuMA | 10 | 10:90 | 7 | >99 | 16000 | 15000 |
| 12 | nBuMA | 17 | 10:50 | 5 | >99 | 10000 | 8500 |
| 13 | HPMA | 10 | 10:90 | 23 | >99 | 16000 | 14000 |
| 14 | HPMA | 17 | 10:50 | 21 | >99 | 10000 | 9500 |
| 15 | DHPMA | 33 | 10:20 | 72 | >99 | 6200 | 6000 |

nBuMA = n-Butyl methacrylate

HPMA = Hydroxypropyl methacrylate

DHPMA = Dihydroxypropyl methacrylate

**Examples 16 to 18: Further AB Block Synthesis in Water/Methanol Mixtures**

Further examples of AB block copolymeriations of MPC as block A were conducted using the ATRP method and under the general conditions indicated in the heading to Table 4. The comonomers for the second block and the relative levels, as well the solvent type the reaction times, the product and intermediate homopolymer characteristic and some of the polydispersities are also shown in Table 4.

## Table 4 - Synthesis of MPC based diblock copolymers via ATRP

[MPC] = 0.67M, [OEG-Br]:[CuCl]:[bipy] = 1:1:2, T = 20°C; MPC polymerised first in all cases

| comonomer | MPC in copolymer (mol%) | Target Dp | Solvent | Time for 100% Conversion | | Mn (AGPC) | | Mw / Mn | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | MPC homopolymer (mins) | Diblock copolymer (h) | MPC homopolymer | Diblock copolymer | MPC homopolymer | Diblock copolymer |
| DHPMA (Ex 16) | 33 | 10:20 | MeOH : H₂O (50 : 50) | 105 | 24 | 2900 | - | 1.18 | 1.43 |
| HEMA (Ex 17) | 33 | 10:20 | MeOH : H₂O (50 : 50) | 150 | 24 | 3000 | - | 1.19 | - |
| DMAEMA (Ex 18) | 50 | 20:20 | H₂O | 100 | 20 | 5900 | 9000 | 1.20 | 1.42 |

DMAEMA = Dimethylaminoethyl methacrylate

### Example 19: ABC Triblock copolymer of MPC and HEMA

A triblock copolymer was synthesised with MPC forming the first (A) and third (C) homopolymer blocks, using OEGBr as the initiator in a 50:50 water: methanol solvent. MPC was used in an amount to give a target Dp for each block of 10. The monomer used to make homopolymer block B was 2-hydroxy ethylmethacrylate which was used in an amount to give a target Dp of 20. It was found that about 100% conversion for the first block occurred in 1.5 hours, for the second in about 2.5 hours and for the third in about 18.5 hours. The calculated Mn for A, AB and ABC were respectively, 3000, 5600 and 8500, whilst the measured Mn values (by NMR) were 2900, 5500 and 8420.

### Examples 20 and 21: Oligomeric Difunctional Initiator

A difunctional inhibitor, a polypropylene oxide having two terminal bromine substituents (MW about 2000), was used to form two polymers, each by carrying out a single step ATRP process with a single monomer, that is MPC (1), and using methanol as the solvent. The process was conducted using 0.67M 1, 0.067 M CuCl transition metal compound, 0.135 M bipyridine and sufficient initiator to provide a polymer with a degree of polymerisation of each block of MPC polymer of 10, for example 20, and a degree of polymerisation of 20 for examples 21. The calculated Mn for the two examples were 7940 and 13900, respectively. The time for about 100% conversions were, respectively 1.5 and 2 hours, whilst the measured values of Mn were 7520 and 11600, respectively.

### Examples 22-29

Table 6 describes the conditions and results for the synthesis of a variety of MPC-DMAEMA and MPC-DEAEMA diblock copolymers by methanolic ATRP. The reaction conditions were [MPC] = 2.02M (6.0g in 10ml methanol), [MPC]: [OEG-Br]:[CuBr]:[bipy] = 30:1:1:2, T = 20°C; MPC was polymerised first in all cases followed by neat DMAEMA (or DEAEMA). Almost complete monomer conversion was achieved after the time indicated in Table 6 for the diblock, as

indicated by ¹H NMR spectroscopy (no residual vinyl double bonds). The reaction mixture was diluted with methanol and passed through a silica column to remove residual ATRP catalyst. After solvent evaporation, the products were dried under vacuum at room temperature.

5

Examples 22-29: Table 6: Data of the polymerization of MPC – DMAEMA or DEAEMA diblock copolymers in methanol

| Ex # | Comonomer | MPC in copolymer (mol %) | TargetDp | [Amine] (M) | Time for > 99% Conversion | | Mn (AGPC) | | Mw / Mn | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | MPC HOMO (mins) | MPC Diblock (h) | MPC(a) HOMO | MPC(b) Diblock | MPC HOMO | MPC Diblock |
| 22 | DEA | 50 | 20:20 | 1.35 | 180 | 20 | 6200 | 14000 | 1.15 | 1.22 |
| 23 | DEA | 33 | 10:20 | 1.35 | 180 | 21 | 3500 | 11000 | 1.17 | 1.29 |
| 24 | DEA | 50 | 30:30 | 2.02 | 130 | 20 | 10000 | 21000 | 1.18 | 1.30 |
| 25 | DEA | 33 | 30:60 | 4.04 | 130 | 22 | 11000 | 31000 | 1.19 | 1.29 |
| 26 | DEA | 23 | 30:100 | 6.73 | 130 | 23 | 11000 | 43000 | 1.19 | 1.28 |
| 27 | DMA | 50 | 30:30 | 2.02 | 120 | 20 | 11000 | 22000 | 1.16 | 1.27 |
| 28 | DMA | 33 | 30:60 | 4.04 | 120 | 24 | 10000 | 34000 | 1.15 | 1.29 |
| 29 | DMA | 23 | 30:100 | 6.73 | 120 | 48 | 11000 | 46000 | 1.18 | 1.32 |

DMA    =    dimethylaminoethylmethacrylate

DEA    =    diethylaminoethylmethacrylate

AGPC    =    aqueous gel permeation chromatography

**Example 30: Reversible pH-Induced Micellisation for Polymer Example 24.**

Micelles with DEAEMA cores were obtained by careful adjustment of the solution pH. The MPC-DEAEMA diblock copolymers dissolved in dilute

5      DCl or NaOD at 20 °C to produce a 1.0 w/v % copolymer solution with a final pH of 1.37 and 8.68 respectively. Fig. 8 shows the proton NMR spectra obtained for the MPC - DEAEMA diblock copolymer at pH 1.37 and 8.68 respectively.

Careful addition of dilute DCl to the MPC-DEAEMA diblock copolymer

10     solution produced a final pH of 1.37. Thus this copolymer dissolved molecularly in dilute aqueous solution at pH 1.37 and 20 °C, since both the MPC and DEAEMA blocks are hydrophilic under these conditions. It can be characterised by proton NMR spectra in Fig. 8a, in where the resonance at $\delta$ 1.25 and $\delta$ 3.4 ppm that was assigned to the residual protons of DEA are

15     presented.

Comparing Figure 8, it is clear that the signals due to the DEAEMA residues at $\delta$ 1.25 and $\delta$ 3.4 ppm have almost disappeared, indicating much lower mobility and decreased solvation for this block. On the other hand, the signals due to the MPC block at $\delta$ 4.0 and $\delta$ 3.5 ppm are still prominent,

20     indicating that this block forms the solvated micellar corona. Micelles comprising DEAEMA cores and MPC corona were formed as expected at pH 8.68 or higher.

Self-assembly was completely reversible: addition of acid resulted in instantaneous micellar dissolution.

25

**Example 31: MPC-Based Macromomer by (aq) ATRP using a Functional Initiator.**

A two-neck round-bottom 100 ml flask was charged with vinyl functional initiator 1 (shown in Figure 9), Cu(I)Br and bipy. Water (10.0 ml)

30     was added and the mixture was stirred until a homogeneous solution was

obtained. MPC monomer (2.0 g) was added to the reaction solution and the flask was sealed with a rubber septum. The reaction mixture was maintained under dry nitrogen and at 20 °C for the duration of the polymerisation. The molar ratio of [MPC]:[initiator]:[CuBr]:[bipy] used in this case was 10:1:1:2,

5    i.e. the target Dp was 10.

**Table 7 indicates the Mn and Mw values established for the reaction mixture after various reaction periods and at completion of polymerisation**

10

| No | Time ( min. ) | Conv. ( % ) | Mn ( theory ) | Mn ( NMR ) | Mw / Mn |
|----|------|------|------|------|---------|
| 1 | 1 | 25 | 770 | 730 | 1.22 |
| 2 | 2 | 33 | 1000 | 960 | 1.23 |
| 3 | 5 | 39 | 1200 | 1100 | 1.23 |
| 4 | 10 | 54 | 1700 | 1600 | 1.24 |
| 5 | 30 | 81 | 2500 | 2100 | 1.25 |
| 6 | 60 | 86 | 2900 | 2400 | 1.26 |
| 7 | 120 | 99 | 3100 | 2500 | 1.27 |

20    Fig. 9 shows the ^{1}H NMR spectra of the initiator, monomer used in the project and the polymer obtained here. As can be seen from Fig. 10 which shows the [1]Hnmr spectra during polymerisation, the area of the polymer peak at $\delta 1$ ppm increased gradually with time while the peak area due to the monomer vinyl signals at $\delta 5.5 - 6.0$ ppm decreased with time. The initiator's

25    vinyl acetate peaks at $\delta 5$ and $\delta 4.75$ ppm due to $CH_2=$ and the peaks at $\delta 7.1$ ppm correspond to $=CH-O-$ remained through the polymerization process.

The aqueous GPC traces of the final polymer and intermediate polymer obtained indicate the peaks corresponding to the polyMPC and the peaks from residual MPC monomer. The monomer peak disappeared when

30    monomer conversion reached over 99 per cent, suggestion the complete conversion of the monomer.

### Example 32: Polymerisation of a Statistical Quatro-Polymer *via* ATRP.

An experimental procedure similar to that for Example 27 was adopted, except that for the statistical quatro-polymer $MPC_{0.30}nBuMA_{0.50}HPMA_{0.15}TMSPMA_{0.05}$ all of the monomers were added together at the beginning of the polymerization. TMSPMA is trimethoxysilylpropylmethacrylate. The concentration of MPC was 2.02M and the ratios are given in moles. The concentration of OEG-Br was $6.73 \times 10^{-2}$ and [OEG-Br]:[CuBr]: [bipy] is 1:1:2. Target Dp is 100. NMR after completion of polymerisation indicated no residual comonomers (absence of vinyl signals between $\delta 5.0 - 6.5$ ppm). No GPC analysis was possible with this copolymer due to the presence of the reactive silyl groups.

### Example 33: AB-Diblock MPC-DMAME Copolymer Formation *via* ATRP.

MPC was block copolymerised with the methyl chloride quaternised derivative of DMA (DMAME). MPC (6.0 g, $2.02 \times 10^{-2}$ mol) was homopolymerised first in a solvent mixture (2 ml methanol + 8 ml water); [MPC]:[OEG-Br]:[CuBr]:[bipy] = 30:1:1:2, target Dp = 30. After 60 mins, the monomer conversion reached > 99%, and the MPC homopolymer obtained had a low polydispersity (Mw / Mn < 1.20). DMAME monomer (4.16 g, $2.02 \times 10^{-2}$ mol, target Dp = 30) was then added to the polymerising solution. After 46 h, a block copolymer with a monomer conversion of more than 99% was obtained, as indicated by $^1H$ NMR spectroscopy (no residual vinyl double bonds at $\delta 5.5 - 6.0$ ppm.

### Example 34: AB-Diblock MPC-DMABZ Copolymer Formation *via* ATRP.

Another block copolymer was prepared in a similar fashion to Example 33, first MPC (6.0 g, $2.02 \times 10^{-2}$ mol) was homopolymerised in 10.00 ml of a 20/80 vol/vol methanol/water mixture such that the molar ratios of [MPC]:[OEG-Br]:[CuBr]:[bipy] were 30:1:1:2 with a target Dp = 30, at 60 mins (99 % monomer conversion) a degassed benzyl chloride derivative of DMA [DMABZ] monomer (5.71 g, $2.02 \times 10^{-2}$ mol, target Dp = 30) was then added to the polymerising aqueous solution. 50 hours after the addition of the

second monomer, ¹H NMR spectroscopy was used to determine an overall conversion of more than 96 % for the diblock copolymer.

## Example 35: AB-Diblock PSSNa-MPC Copolymer Formation *via* ATRP.

5 Sodium 4-styrenesulfonate (SSNa) was typically polymerised first, as follows: The SSNa monomer (4.17 g) was dissolved in a mixed solvent (15 ml $H_2O$ + 5 ml MeOH), the pH was adjusted to about 10-12 with NaOH and the solution was degassed. The sodium 4-(bromomethyl)benzoate initiator (NaBMB) was added, together with the bipy ligand and Cu(I)Cl such that the

10 [SSNa]:[NaBMB]:[CuCl]:[bipy] molar ratio was 50:1:1:2 and the target Dp was 50. After 120 mins, the SSNa monomer conversion reached 95 % and the second monomer, MPC, was then added as a solid (6.0 g, 2.02 ×10⁻² mol; target Dp = 50) to the polymerising SSNa solution. More than 99 % MPC conversion was achieved after 22 h, as indicated by ¹H NMR spectroscopy

15 (no residual vinyl double bonds at δ 5.5 – 6.0 ppm).

## Example 36-37: AB-Diblock MPC-PPO Copolymer Formation *via* ATRP.

Block copolymerisation of MPC was achieved using a poly(propylene glycol) [PPO] macro-initiator: MPC (6.0 g, 2.02 ×10⁻² mol) was polymerised in

20 10.0 ml methanol. The molar ratios of [MPC]:[PPO-Br]:[CuBr]:[bipy] were 30:1:1:2. After 12 h, the MPC conversion reached 100 %, as indicated by ¹H NMR spectroscopy (no residual vinyl double bonds at δ 5.5 – 6.0 ppm).

Another MPC-PPO block copolymer was also synthesised with a longer MPC block under the following conditions: MPC (6.24 g, 2.10 ×10⁻²

25 mol); [MPC]:[PPO-Br]:[CuCl]:[bipy] = 50:1:1:2.5. A diblock copolymer with a monomer conversion of 100 % was obtained after 18 h.

## Example 38-43: MPC-Based Copolymers Formation via ATRP

Table 8 summarises the conditions and results from MPC diblock

30 copolymer syntheses. The reaction conditions were [MPC] = 2.02 M, [OEG-Br]:[CuBr] : [bipy] = 1 : 1 : 2, T = 20°C; MPC was polymerised first in all cases. The second block was formed either of diethylaminoethyl

methacrylate (DEA) or ammonium-2-sulphatoethylmethacrylate (SEM).

### Table 8: Data for the MPC-based copolymers

| Ex # | Target Composition | Solvent composition | [Second Monomer] (mol dm$^{-3}$) | Time for > 99% Conversion | |
|------|--------------------|---------------------|------------------------------------|------------------------------|--|
| | | | | MPC Homo (mins) | MPC Diblock (h) |
| 38 | $MPC_{50}$ - $DEA_{50}$ | MeOH | 2.02 | 100 | 24 |
| 39 | $MPC_{50}$ - $DEA_{100}$ | MeOH | 4.04 | 100 | 46 |
| 40 | $MPC_{30}$ - $DEA_{40}$ | MeOH | 2.69 | 70 | 19 |
| 41 | $MPC_{30}$ – $DEA_{50}$ | MeOH | 3.37 | 70 | 43 |
| 42 | $MPC_{30}$ – $DEA_{70}$ | MeOH | 4.71 | 70 | 46 |
| 43 | $MPC_{50}$ – $SEM_{50}$ | $H_2O$ | 2.02 | 40 | 24 |

**Example 44-47: Homopolymerisation of MPC in MeOH via ATRP using new functional initiators and a PPO-based macro-initiator**

Table 9 describes the conditions and results from MPC homopolymer sytheses. The reaction conditions were [MPC] = 2.02 x 10$^{-2}$ mol (examples 44, 46, 47), [MPC] = 1.35 x 10$^{-2}$ mol (example 45), [OEG-Br] : [CuBr] : [bipy] = 1 : 1 : 2, T = 20°C.

### Table 9: Data for the MPC homopolymers

| Ex # | Target Composition | Solvent composition | [Initiator] (mol dm$^{-3}$) | Time for > 99% Conversion (h) |
|------|--------------------|---------------------|-------------------------------|--------------------------------|
| 44 | $PEG_{45}$ - $MPC_{40}$ | MeOH | 5.05 | 24 |
| 45 | $PEG_{45}$ - $MPC_{10}$ | MeOH | 1.35 | 3 |
| 46 | DMAEBr – $MPC_{20}$ | MeOH | 0.10 | 3 |
| 47 | MEBr – $MPC_{50}$ | MeOH | 0.04 | 3 |

DMAEBr : This is a functional initiator for macromonomer syntheses. It was synthesised as follows:
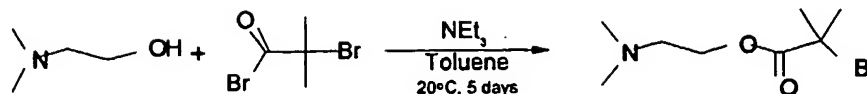
MEBr : An NMR-labelled initiator. It was synthesised according to:
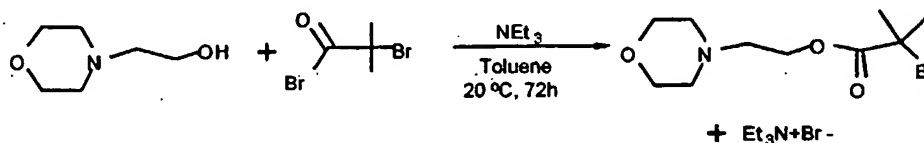


## Example 48: MPC-Based Macromonomer *via* ATRP.



Derived from DMAEBr initiator
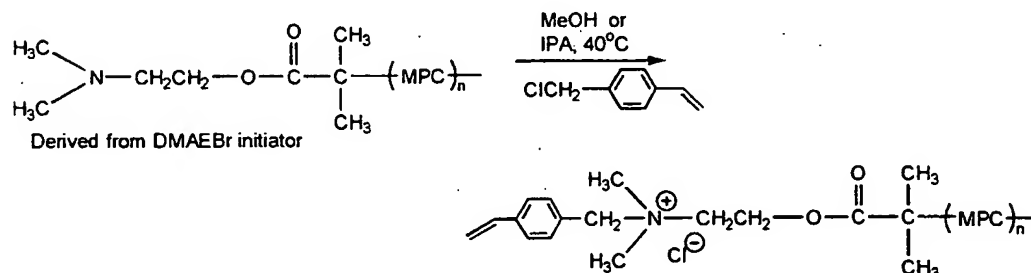
5

The MPC polymer obtained in Example 46 was reacted with 4-vinylbenzyl chloride [4-VBZCl] in methanol at 40 °C. The vinyl benzylchloride quaterises the tertiary amine group at the terminal of the MPC polymer. The molar ratios of [MPC polymer] : [4-VBZCl] were 1:2. A macromonomer was

10    obtained after five days. This macromonomer was contaminated with residual 4-VBZCl, as indicated by $^1$H NMR spectroscopy. The peaks at $\delta$ 5.5 – 6.0 ppm and $\delta$ 6.5 – 7.0 ppm are due to the vinyl and aromatic groups of the 4-VBZCl, respectively. Therefore the resulting macromonomer required further purification by washing with THF.

15

## Example 49-50: A(BC)-Diblock MPC-(MMA / DEA) Copolymer Formation *via* ATRP.

MPC was block copolymerised with MMA / DEA. MPC (6.0 g, $2.02 \times 10^{-2}$ mol) was homopolymerised first in 10ml methanol; [MPC]:[OEG-Br]:[CuBr]:[bipy] = 30:1:1:2, target Dp = 30. After 60 mins, the monomer conversion reached > 99%, and the homopolymer obtained had a low

5      polydispersity (Mw / Mn < 1.20). MMA monomer (1.35g, $1.35 \times 10^{-2}$ mol, target Dp = 20) and DEA monomer (5.0g, $2.70 \times 10^{-2}$ mol, target Dp = 40) was then added to the polymerising solution. After 24 h, a block copolymer with a monomer conversion of more than 99% was obtained. The reaction mixture was diluted with methanol and passed through a silica column to remove

10      residual ATRP catalyst. After solvent evaporation, the products were dried under vacuum at room temperature. For example 50, the MMA / DEA ratio was changed to 40 / 20.

**Example 51: AB-Diblock MPC-HEMA Copolymer Formation *via* ATRP.**

15      Another block copolymer was prepared in a similar fashion to Example 49, first MPC (6.0g, $2.02 \times 10^{-2}$ mol) was homopolymerised in 10.00 ml of the methanol such that the molar ratios of [MPC]:[OEG-Br]:[CuBr]:[bipy] were 50:1:1:2 with target Dp = 50. After 100 mins (99% monomer conversion) a degassed HEMA monomer (2.1g, $1.62 \times 10^{-2}$ mol, target Dp = 40) was then

20      added to the polymerising aqueous solution. 20 hours after the addition of the second monomer, $^1$H NMR spectroscopy was used to determine an overall conversion of more than 99% for the diblock copolymer. A white diblock copolymer (Mn = 16,000) was obtained with a relatively low polydispersity (Mw/Mn ~ 1.25).

25

**Example 52: AB-Diblock MPC-CBMA Copolymer Formation *via* ATRP.**

MPC (6.0 g, $2.02 \times 10^{-2}$ mol) was polymerised first in methanol (10 ml) under the following conditions: [MPC]:[OEG-Br]:[CuBr]:[bipy] = 100:1:1:2; target Dp = 100. After 120 mins, the monomer conversion reached almost

30      100 % with Mn = 31,000 and Mw/Mn = 1.16, as judged by aqueous GPC. The second monomer, N-methacryloyloxyethyl-N,Ndimethylammoniummethyl carboxylate inner salt CBMA (carboxybetaine methacrylate) was then added

(4.82 g, 2.02×10$^{-2}$ mol; target Dp = 100) to the polymerizing MPC solution. Almost complete monomer conversion was achieved after 24 hours, as indicated by $^1$H NMR spectroscopy (no residual vinyl double bonds). A white diblock copolymer (Mn = 33,000) was obtained with a relatively low polydispersity (Mw/Mn ~ 1.20).

**Example 53: AB-Diblock MPC-MMA Copolymer Formation *via* ATRP.**

Block copolymerisation of MPC with MMA. MPC (6.0 g, 2.02×10$^{-2}$ mol, target Dp = 100) was polymerised in 10.0 ml methanol. The molar ratios of [MPC]:[OEG-Br]:[CuBr]:[bipy] were 100:1:1:2. After 3 hours, the monomer conversion reached more than 99%, as indicated by $^1$H NMR spectroscopy (no residual vinyl double bonds at δ5.5 – 6.0 ppm). MMA monomer (0.6g, 6.06×10$^{-3}$ mol, target Dp = 30) was then added to the polymerising solution. After 24 h, a block copolymer with a monomer conversion of more than 99% was obtained. The reaction mixture was diluted with methanol and passed through a silica column to remove residual ATRP catalyst. After solvent evaporation, the products were dried under vacuum at room temperature.

**Examples 54 and 55: MPC-DMA-DEA ABC Triblock Copolymers Formation via ATRP**

MPC (6.0 g, 2.02×10$^{-2}$ mol) was polymerised first in methanol (10 ml) under the following conditions: [MPC]:[OEG-Br]:[CuBr]:[bipy] = 30:1:1:2; target Dp = 30. After 60 min, the monomer conversion reached 99 % with Mn = 10,000 and Mw/Mn = 1.19, as judged by aqueous GPC. The second monomer, DMA was then added as a liquid (2.15 g, 1.35×10$^{-2}$ mol; target Dp = 20) to the polymerising solution. Essentially 98 % monomer conversion was achieved after 150 min, as indicated by $^1$H NMR spectroscopy. DEA was then added as the third monomer (5.05 g, 2.70×10$^{-2}$ mol, target Dp = 40) to the polymerising solution. After 48 h, a block copolymer with an Mn of 20,000 and a polydispersity of 1.43 was obtained.

A MPC 30-DMA20-DEA.30 triblock copolymer was polymerised using the same procedure with an appropriate adjustment to the level of DEA.

### Example 56: Polymerisation of An MPC-Vinylacetate Functional Macromonomer (Example 31).

The MPC-based macromer (0.5g) described in example 31 was dissolved in methanol (10g) containing 0.5wt% Perkadox 16 initiator. The

5  solution was stirred at reflux for 4 hours after which the reaction mixture was allowed to cool. The solution was sampled and the solvent removed to yield a white solid. This was redissolved in $D_2O$ and subjected to $^1H$ NMR and compared to the spectrum of the macromer. The polymerised product showed no vinyl bonds at 5.5 and 6.0 ppm, demonstrating that the vinyl

10  acetate reactive chain end group can be polymerised to produce a comb-like poly-MPC polymer.

### Example 57: Shell-crosslinking of MPC30-DMA20-DEA30:

The a MPC30-DMA20-DEA30 triblock copolymer formed in Example

15  55 was micellised as in Example 30. The intensity-average micelle diameter was found to be 56 nm as a 1 wt. % aqueous solution at pH 9.6 (polydispersity 0.064 - which is good).

This was shell-crosslinked in solution by addition of 1,2-bis(2-iodoethoxy)ethane (BIEE) at pH8-9 for 3 days at 20°C with a BIEE:DMA ratio

20  0.5mol ratio (target crosslinking); this reacts to quaternise and cross-link the DMA residues. After shell-crosslinking of this triblock copolymer, the micelles are 63 nm diameter (polydispersity 0.08) at pH 9.6 and 67 nm (polydispersity 0.111) at pH 2.0. The latter measurement is a proof that the shell cross-linking was successful, since non-crosslinked micelles dissociate

25  in acidic media.

### Example 58: Polymerisation of (MPC30-HPMA15-TMSPMA5)-(BMA50) Block Quatro polymer:

The polymer of (MPC30-HPMA15-TMSPMA5)-(BMA50) was made

30  according to the process outlined in example 32, except the MPC, HPMA and TMSPMA were added together and polymerised statistically to 99%

conversion before final addition of the BMA to form a separate block of hydrophobe in the copolymer.

**Example 59: Drug Delivery Studies**

5      Steel coupons coated with example 32 (statistical quatro polymer) and example 58 (block quatro polymer) and cured overnight at 70°C. The coupons were then immersed in a 10mg/ml solution of dexamethasone in either ethanol or ethanol:hexane (3:1) for 30 minutes. The coupons were removed and allowed to air dry for a further 30 minutes before being eluted

10      into 5ml of ethanol using sonication. The ethanol solution was then analysed by UV spectroscopy at 243nm to detect the dexamethasone eluant. Figure 11 shows the relative amounts of drug loaded from the two solutions using the two polymers. Loading from ethanol or ethanol:hexane had no statistically significant difference on the total loading of drug in the statistical

15      quatro polymer (example 32). The was, however, as statistically significant increase (p=0.04) for the block quatro polymer, indicating that the hexane co-solvent was able to access and swell the hydrophobic blocks and increase the drug loading relative to the ethanol-swollen sample.

      Similarly, when the same polymers were loaded from the mixed

20      ethanol:hexane solution and eluted in a kinetic experiment over 300 minutes, a higher final absorbance was recorded for the block quatro polymer, indicating more effective loading into the polymer coating by the solvent combination than for the statistical quatro-polymer coating (Figure 12).

25      **Examle 60: Performance data**

      Some of the polymers made above were subjected to tests to determine whether they reduce the level of fibrinogen absorption. This is an indicator of haemocompatibility.

      Fibrinogen ELISA was performed as previously described in WO-A-

30      9301221. All polymers as indicated in Table 10 were dip-coated onto polyethylene terephthalate (PET) strips (30mm x 10mm) at 3mm/sec from ethanolic solutions (10mg/ml). The cross-linkable polymer (Example 32) was

crosslinked at 70°C overnight prior to testing. The positive control coating
was an MPC-laurylmethacrylate (1:2) copolymer made by conventional free
radical polymerisation and described in WO-A-9301221 and used
commercially as a biocompatible and haemocompatible coating which
5    reduces the fibrinogen absorption.

Table 10

| Example | Coating | Mean Abs @ 450 | S.D. | %CV | % Reduction | t-Test |
|---------|---------|----------------|------|-----|-------------|--------|
| 60.1.1 | No coating | 0.797 | 0.053 | 6.6 | - | - |
| 60.1.2 | Control | 0.136 | 0.012 | 8.9 | 83 | 0.000 |
| 60.1.3 | Polymer 25 | 0.116 | 0.015 | 11.6 | 85.5 | 0.000 |
| 60.1.4 | Polymer 26 | 0.189 | 0.03 | 13.4 | 76.3 | 0.000 |
| 60.2.1 | No coating | 0.909 | 0.117 | 12.9 | - | - |
| 60.2.2 | Control | 0.175 | 0.021 | 12 | 80.8 | 0.000 |
| 60.2.3 | Polymer 32 | 0.19 | 0.028 | 14.8 | 79.1 | 0.000 |

These data indicate that the simple block copolymers of examples 25
and 26 can be molecularly dissolved in an alcohol and physi-adsorbed onto
planar surfaces to form stable biocompatible coatings. The statistical quatro
20    polymer of example 32 can be coated and cured to form a stable
biocompatible coating.

25

30

## Claims

1. A polymerisation process in which ethylenically unsaturated monomers including a zwitterionic monomer of the general formula I

Y B X         I

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,



A is -O- or $NR^1$;

$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n SO_3-$ in which n is 1 to 12;

$A^2$ is selected from a bond, -O-, O-CO-, CO-O, $CO-NR^1-$, $-NR^1-CO$, $O-CO-NR^1-$, $NR^1-CO-O-$;

R is hydrogen or $C_{1-4}$ alkyl;

$R^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

$R^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;

X is an ammonium phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group.

are polymerised by a living radical polymerisation process in the presence of an initiator, and a catalyst.

2. A polymerisation process according to claim in which X is a group of the general formula II
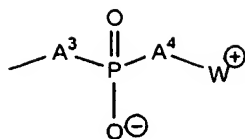
$$\underset{\substack{|\\ O^{\ominus}}}{\overset{\substack{O\\ \|}}{-A^3-\underset{}{P}-A^4-W^{\oplus}}} \qquad\qquad II$$

5        in which the moieties $A^3$ and $A^4$, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and $W^+$ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a $C_{1-12}$- alkanediyl group,

10        preferably in which $W^+$ is a group of formula $-W^1-N^+R^3_3$, $-W^1-P^+R^4_3$, $-W^1-S^+R^4_2$ or $-W^1-Het^+$ in which:

$W^1$ is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene

15        aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group $W^1$ optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups $R^3$ are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or

20        two of the groups $R^3$ together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups $R^3$ together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups $R^3$ is substituted by a

25        hydrophilic functional group, and

the groups $R^4$ are the same or different and each is $R^3$ or a group $OR^3$, where $R^3$ is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

30        3.       A polymerisation process according to claim 2 in which X is a group of general formula III
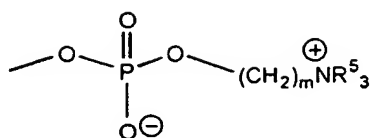
$$-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^{\ominus}}{|}}{P}}-O-(CH_2)_m\overset{\oplus}{N}R^5_3 \qquad \text{III}$$

5    where the groups $R^5$ are the same or different and each is hydrogen or $C_{1-4}$ alkyl, and m is from 1 to 4, in which preferably the groups $R^5$ are the same preferably methyl.

4.    A polymerisation process according to claim 1 in which X is a group having the general formula IV

10

$$-A^5-R^6-\overset{\oplus}{W^2}(R^7)-R^8-A^6-\overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\underset{\displaystyle O}{\|}}{P}}-R^9 \qquad \text{IV}$$
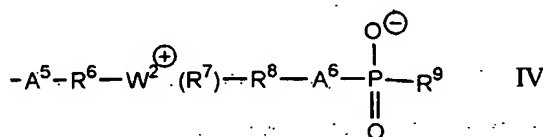
in which $A^5$ is a valence bond, -O-, -S- or -NH-, preferably -O-;

15    $R^6$ is a valence bond (together with $A^5$) or alkanediyl, -C(O)alkylene- or -C(O)NH alkylene preferably alkanediyl, and preferably containing from 1 to 6 carbon atoms in the alkanediyl chain;

$W^6$ is S, $PR^7$ or $NR^7$;

the or each groups $R^7$ is hydrogen or alkyl of 1 to 4 carbon atoms or

20    the two groups $R^7$ together with the heteroatom to which they are attached form a heterocyclic ring of 5 to 7 atoms;

$R^8$ is alkyanediyl of 1 to 20, preferably 1 to 10, more preferably 1 to 6 carbon atoms;

$A^6$ is a bond, NH, S or O, preferably O; and

25    $R^9$ is a hydroxyl, $C_{1-12}$ alkyl, $C_{1-12}$ alkoxy, $C_{7-18}$ aralkyl, $C_{7-18}$ -aralkoxy, $C_{6-18}$ aryl or $C_{6-18}$ aryloxy group.

5.    A polymerisation process according to claim 4 in which

$A^5$ is a bond;

$R^6$ is a $C_{2-6}$ alkanediyl;

30    $W^2$ is $NR^7$:

each $R^7$ is $C_{1-4}$ alkyl;

$R^8$ is $C_{2-6}$ alkanediyl;

$A^6$ is O; and

$R^9$ is $C_{1-4}$ alkoxy.

6.      A polymerisation process according to any preceding claim in which Y is $H_2C=CR-CO-A-$ in which R is hydrogen or methyl and A is O.

7.      A polymerisation process according to any preceding claim in which B is a straight chain $C_{2-6}$ -alkanediyl.

8.      A polymerisation process according to claim 1 in which the zwitterionic monomer is 2-methacryloyloxyethyl-2'- trimethylammonium ethyl phosphate inner salt.

9.      A polymerisation process according to any preceding claim in which the polymerisation mixture contains a non-polymerisable solvent, preferably in an amount, in the range of 10 to 500% by weight based on the weight of ethylenically unsaturated monomer.

10.      A polymerisation process according to claim 9 in which the solvent comprises water, preferably in an amount in the range 10 to 100% by weight based on the weight of ethylenically unsaturated monomer.

11.      A polymerisation process according to any preceding claim in which the ethylenically unsaturated monomer includes at least one comonomer, preferably selected from anionic, cationic and non-ionic monomers, more preferably comprising a non-ionic monomer.

12.      A polymerisation process according to claim 11 in which the comonomer is immiscible with the zwitterionic monomer, and in which the polymerisation mixture comprises a non-polymerisable solvent in which both the zwitterionic monomer and the comonomer are soluble.

13.      A polymerisation process according to claim 12 in which the solvent includes water and a water-miscible organic solvent, preferably a $C_{1-4}$ alkanol, more preferably methanol.

14.      A polymerisation process according to any preceding claim which is an atom or group transfer radical polymerisation.

15.      A polymerisation process according to claim 14, in which the initiator has a radically transferable atom or group, and the catalyst comprises a transition metal compound and a ligand, in which the transition

metal compound is capable of participating in a redox cycle with the initiator
and dormant polymer chain, and the ligand is either any N-, O-, P- or S-
containing compound which can coordinate with the transition metal atom in
a σ-bond, or any carbon-containing compound which can coordinate with the
5　transition metal in a π-bond, such that direct bonds between the transition
metal and growing polymer radicals and not formed.

　　　　16.　A polymerisation process according to claim 15 in which the
initiator is of the general formula V

10　　　　　　　　　　$R^{11}R^{12}R^{13}C\text{-}X^2$　　　　　　　　　　V


　　where:

　　$X^2$ is selected from the group consisting of Cl, Br, I, $OR^{10}$, $SR^{14}$, $SeR^{14}$,
$OP(=O)R^{14}$, $OP(=O)(OR^{14})_2$, $O\text{-}N(R^{14})_2$ and $S\text{-}C(=S)N(R^{14})_2$, where $R^{10}$ is alkyl
15　of from 1 to 20 carbon atoms in which each of the hydrogen atoms may be
independently replaced by halide, $R^{14}$ is aryl or a straight or branched $C_1\text{-}C_{20}$
alkyl group, and where an $N(R^{14})_2$ group is present, the two $R^{14}$ groups may
be joined to form a 5- or 6-membered heterocyclic ring; and

　　　　$R^{11}$, $R^{12}$ and $R^{13}$ are each independently selected from the group
20　consisting of H, halogen, $C_1\text{-}C_{20}$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C(=O)R^{15}$,
$C(=O)NR^{16}R^{17}$, COCl, OH, CN, $C_2\text{-}C_{20}$ alkenyl, $C_2\text{-}C_{20}$ alkenyl oxiranyl,
glycidyl, aryl, heterocyclyl, aralkyl, aralkenyl, $C_1\text{-}C_6$ alkyl in which from 1 to
all of the hydrogen atoms are replaced with halogen, and $C_1\text{-}C_6$ alkyl
substituted with from 1 to 3 substituents selected from the group consisting of
25　$C_1\text{-}C_4$ alkoxy, aryl, heterocyclyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, $\text{-}CR^{12}R^{13}X^2$,
oxiranyl and glycidyl;

　　　　where $R^{15}$ is alkyl of from 1 to 20 carbon atoms, alkoxy of from 1 to 20
carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 3 carbon
atoms, aryloxy or heterocyclyloxy any of which groups may have substituents
30　selected from optionally substituted alkoxy, oligoalkoxy, amino (including
mono- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn

may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups; and

$R^{16}$ and $R^{17}$ are independently H or alkyl of from 1 to 20 carbon atoms which alkyl groups, in turn may have substiuents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy, or $R^{16}$ and $R^{17}$ may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring;

such that not more than two of $R^{11}$, $R^{12}$ and $R^{13}$ are H.

17. The process of claim 16, wherein no more than one of $R^{11}$, $R^{12}$ and $R^{13}$ is H.

18. A polymerisation process according to claim 16 in which $X^2$ is selected from Cl, Br or I, preferably Br.

19. A polymerisation process according to any of claims 16 to 18 in which $R^{11}$ and $R^{12}$ are each methyl and $R^{13}$ is -CO-$R^{15}$ in which $R^{15}$ is oligoalkoxy, preferably methoxy-oligoethoxy in which there are 2 to 10 ethoxy groups.

20. A polymerisation process according to any of claims 15 to 19 in which the transition metal compound $M_t^{n+}X'_n$, where:

$M_t^{n+}$ may be selected from the group consisting of $Cu^{1+}$, $Cu^{2+}$, $Fe^{2+}$, $Fe^{3+}$, $Ru^{2+}$, $Ru^{3+}$, $Cr^{2+}$, $Cr^{3+}$, $Mo^{2+}$, $Mo^{3+}$, $W^{2+}$, $W^{3+}$, $Mn^{2+}$, $Mn^{3+}$, $Mn^{4+}$, $Rh^{3+}$, $Rh^{4+}$, $Re^{2+}$, $Re^{3+}$, $Co^+$, $Co^{2+}$, $Co^{3+}$, $V^{2+}$, $V^{3+}$, $Zn^+$, $Zn^{2+}$, $Ni^{2+}$, $Ni^{3+}$, $Au^+$, $Au^{2+}$, $Ag^+$ and $Ag^{2+}$;

X' is selected from the group consisting of halogen, $C_{12}$-$C_6$-alkoxy, $(SO_4)_{\frac{1}{2}}$, $(PO_4)_{1/3}$, $(R^{18}PO_4)\frac{1}{2}$, $(R^{18}{}_2PO_4)$, triflate, hexafluorophosphate, methanesulphonate, arylsulphonate, CN and $R^{19}CO_2$, where $R^{18}$ is aryl or a straight or branched $C_{1-20}$ alkyl and $R^{19}$ is H or a straight or branched $C_1$-$C_6$ alkyl group which may be substituted from 1 to 5 times with a halogen; and

n is the formal charge on the metal ($0 \le n \le 7$).

21. A polymerisation process according to claim 20 in which the metal compound is CuHal or RuHal$_2$ where Hal is chlorine or bromine.

22. A polymerisation process according to any of claims 15 to 20, wherein said ligand is selected from the group consisting of:

a) compounds of the formulas:

$$R^{20}\text{-}Z\text{-}R^{21} \quad \text{and}$$

$$R^{20}\text{-}Z\text{-}(R^{22}\text{-}Z)_m\text{-}R^{21}$$

where:

$R^{20}$ and $R^{21}$ are independently selected from the group consisting of H, $C_1\text{-}C_{20}$ alkyl, aryl, heterocyclyl and $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_4$ dialkylamino, $C(=O)R^{22}$, $C(=O)R^{23}R^{24}$ and $A^7C(=O)R^{25}$, where $A^7$ may be $NR^{26}$ or $O$; $R^{22}$ is alkyl of from 1 to 20 carbon atoms, aryloxy or heterocyclyloxy; $R^{23}$ and $R^{24}$ are independently H or alkyl of from 1 to 20 carbon atoms or $R^{23}$ and $R^{24}$ may be joined together to form an alkanediyl group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring; $R^{25}$ is H, straight or branched $C_1\text{-}C_{20}$ alkyl or aryl and $R^{26}$ is hydrogen, straight or branched; $C_{1\text{-}20}$-alkyl or aryl; or $R^{20}$ and $R^{21}$ may be joined to form together with Z, a saturated or unsaturated ring;

Z is O, S, $NR^{27}$ or $PR^{27}$, where $R^{27}$ is selected from the same group as $R^{20}$ and $R^{21}$, and where Z is $PR^{27}$, $R^{27}$ can also $C_1\text{-}C_{20}$ alkoxy or Z may be a bond $CH_2$ or a fused ring, where one or both of $R^{20}$ and $R^{23}$ is heterocyclyl,

each $R^{22}$ is independently a divalent group selected from the group consisting of $C_1\text{-}C_8$ cycloalkanediyl, $C_1\text{-}C_8$ cycloalkenediyl, arenediyl and heterocyclylene where the covalent bonds to each Z are at vicinal positions or $R^{22}$ may be joined to one or both of $R^{20}$ and $R^{21}$ to formulate a heterocyclic ring system; and

m is from 1 to 6;

b) CO;

c) porphyrins and porphycenes, which may be substituted with from 1 to 6 halogen atoms, $C_{1\text{-}6}$ alkyl groups, $C_{1\text{-}6}$-alkoxy groups, $C_{1\text{-}6}$ alkoxycarbonyl, aryl groups, heterocyclyl groups, and $C_{1\text{-}6}$ alkyl groups further substituted with from 1 to 3 halogens;

d) compounds of the formula $R^{23}R^{24}C(C(=O)R^{25})_2$, where $R^{25}$ is $C_{1\text{-}20}$ alkyl, $C_{1\text{-}20}$ alkoxy, aryloxy or heterocyclyloxy; and each of $R^{23}$ and $R^{24}$ is

independently selected from the group consisting of H, halogen, $C_{1-20}$ alkyl, aryl and heterocyclyl, and $R^{23}$ and $R^{24}$ may be joined to form a $C_{1-8}$ cycloalkyl ring or a hydrogenated aromatic or heterocyclic ring, of which the ring atoms may be further substituted with 1 to 5 $C_{1-6}$ alkyl groups, $C_{1-6}$ alkoxy groups,

5     halogen atoms, aryl groups, or combinations thereof; and

        e)     arenes and cyclopentadienyl ligands, where said cyclopentadienyl ligand may be substituted with from one to five methyl groups, or may be linked through and ethylene or propylene chain to a second cyclopentadienyl ligand.

10     23.     A polymerisation process according to claim 22 in which the ligand is bipyridine, triphenylphosphine, 1;1,4,7,10,10-hexamethyl-triethylene tetramine, or
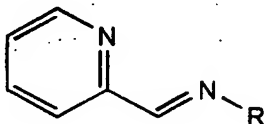


where R is an alkyl or substituted alkyl group, in which the substituent is selected from amino, including alkylamino and acylamino, alkoxy, hydroxy, acyl, acyloxy, alkoxycarbonyl, heterocyclyl, ionic, and halogen substituents.

20     24.     A polymerisation process according to any preceding claim in which the molar ratio of initiator to ethylenically unsaturated monomer is an the range 1:(5 to 500), preferably 1: (10 to 100).

        25.     A polymerisation process according to any preceding claim in which the polymer product has an average degree of polymerisation in the

25     range 5 to 500, preferably 10 to 100.

        26.     A polymerisation process according to any preceding claim in which the polydispersity of the polymer product is less than 1.5.

        27.     A polymerisation process according to any preceding claim which is carried out until the level of residual ethylenically unsaturated

30     monomer is less than 5%.

        28.     A polymerisation process according to claim 27 in which the initial polymer product is subjected to a second step of living radial

polymerisation in which further ethylenically unsaturated monomer is contacted with the initial polymer product which acts as initiator in the presence of a catalyst, to form a block copolymer product.

29. A polymerisation process according to claim 28 in which the initial polymer product is not isolated from the product mixture before the second step.

30. A polymerisation process according to claim 29 in which the further monomers are added to the product mixture of the first step as a solution in a solvent which is miscible with the said product mixture.

31. A polymerisation process according to claim 28 in which the initial polymer product is isolated from the catalyst of the first step, and in which a different catalyst is used in the second step, the catalyst preferably being as defined in claim 15.

32. A polymerisation process according to claim 28 or claim 31 which the first polymerisation is conducted in the presence of a non-polymerisable solvent and in which the initial polymer product is isolated from the solvent, and in which the second step is conducted in the absence of a non-polymerisable solvent or in the presence of a non-polymerisable solvent different from or the same as the solvent used in the first step.

33. A polymer formed from ethylenically unsaturated monomers including a zwitterionic monomer of the general formula I
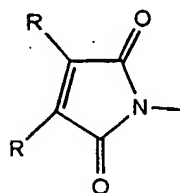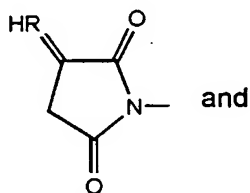
$$Y \; B \; X \qquad I$$

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,



and
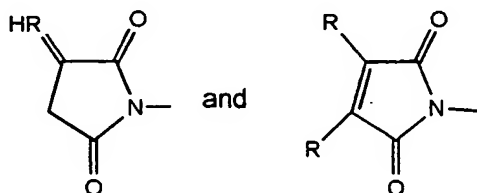
$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n$ $SO_3-$ in which n is 1 to 12;

A is -O- or NR$^1$;

A$^2$ is selected from a bond -O-, O-CO-, CO-O, CO-NR$^1$-, -NR$^1$-CO, O-CO-NR$^1$-, NR$^1$-CO-O-;

R is hydrogen or C$_{1-4}$ alkyl;

R$^1$ is hydrogen, C$_{1-4}$ alkyl or BX.

R$^2$ is hydrogen or C$_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;

X is an ammonium, phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group, having a degree of polymerisation in the range 5 to 500 and a polydispersity of less than 1.5.

34. A polymer according to claim 33 in which the zwitterionic monomer is as defined in any of claims 2 to 8.

35. A polymer according to claim 33 or claim 34 in which the ethylenically unsaturated monomer includes at least one comonomer selected from anionic, cationic and non-ionic monomers, preferably comprising a non-ionic monomer.

36. A polymer according to any of claims 33 to 35 in which the ethylenically unsaturated monomer includes at least one cross-linkable monomer, preferably a monomer comprising a reactive silyl group, more preferably a trialkoxysilylalkyl(alk)acrylate.

37. A polymer according to claim 33 having at least one terminal group or atom which is transferable to produce a radical in the presence of a catalyst which comprises a transition metal compound and a ligand, in which the transition metal compound is capable of participating in a redox cycle with the initiator and dormant polymer chain, and the ligand is either any N-, O-, P- or S- containing compound which can coordinate with the transition metal atom in a σ-bond, or any carbon-containing compound which can coordinate with the transition metal in a π-bond, such that direct bonds between the transition metal and molecules of the polymer are not formed.

38.　A polymer according to claim 37 in which the said terminal atom or group is a halogen atom, preferably a chlorine, or more preferably, a bromine atom.

39.　A polymer according to claim 37 or 38 which has one such terminal group and, at the other end of the polymer chain, has an oligo(alkoxy)alkyl group joined to the end residue derived from the said ethylenically unsaturated monomers.

40.　A polymer according to claim 37 or claim 38 which has one such terminal group and, at the other end of the polymer chain has a functional group joined to the end residue derived from said ethylenically unsaturated monomers.

41.　A polymer according to claim 40 in which the functional group comprises an ethylenically unsaturated group and/or a tertiary or quaternary amine group.

42.　A block copolymer of the A-B or A-B-A type in which A and B are the same or, preferably, different, in which at least one of the A and B is formed from ethylenically unsaturated monomer including a zwitterionic monomer of the general formula VI

Y B X'　　　　　　　　VI

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,

 and 

A is -O- or $NR^1$;

$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n SO_3-$ in which n is 1 to 12;

$A^2$ is selected from a bond -O-, O-CO-, CO-O, CO-NR$^1$-, -NR$^1$-CO, O-CO-NR$^1$-, NR$^1$-CO-O-;

R is hydrogen or $C_{1-4}$ alkyl;

R$^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

R$^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

X$^1$ is a zwitterionic group.

43. A block copolymer according to claim 42 in which the zwitterionic group is an ammonium, sulphonium or phosphonium phosphate or phosphonate ester zwitterionic group.

44. A block copolymer according to claim 42 or 43 in which the zwitterionic monomer has the further features as defined in any of claims 2 to 8.

45. A block copolymer according to any of claims 42 to 44 in which the block comprising zwitterionic monomer is formed from ethylenically unsaturated monomers comprising at least one comonomer selected from cationic, anionic and non-ionic monomers.

46. A block copolymer according to any of claims 42 to 44 in which the degree of polymerisation of the block comprising zwitterionic monomer is in the range 2 to 100, preferably 5 to 50.

47. A block copolymer according to any of claims 42 to 46 in which both blocks A and B are formed from ethylenically unsaturated monomer, the monomers from which A is formed comprising either different monomers to the monomers from which B is formed, or the same monomers as the monomers from which B is formed but in different ratios.

48. A block copolymer according to claim 47 in which one of the blocks is formed from monomers comprising an oligoalkoxy monomer of the general formula VII
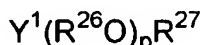
$$Y^1(R^{26}O)_pR^{27} \qquad\qquad VII$$

in which $Y^1$ is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,

5



and
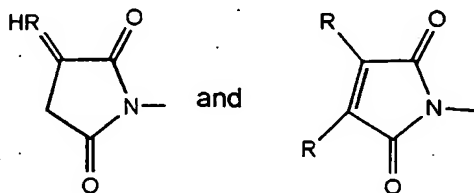
A is -O- or $NR^1$;

10　　$A^1$ is selected from a bond, $(CH_2)_nA^2$ and $(CH_2)_n SO_3-$ in which n is 1 to 12;

$A^2$ is selected from a bond -O-, O-CO-, CO-O, CO-NR$^1$-, -NR$^1$-CO, O-CO-NR$^1$-, NR$^1$-CO-O-;

R is hydrogen or $C_{1-4}$ alkyl;

15　　$R^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

$R^2$ is hydrogen or $C_{1-4}$ alkyl; and

$R^{26}$ is $C_{2-3}$ alkanediyl;

$R^{27}$ is $C_{1-12}$ alkyl, $C_{7-12}$ aralkyl or aryl; and

p is 1 to 50.

20　　49.　　A block copolymer according to claim 48 in which $Y^1$ is $H_2C=CR-CO-A-$ in which R is methyl and A is O.

50.　　A block copolymer according to claim 47 in which the monomers from which A is formed include a first zwitterionic monomer of the formula VI and the monomers from which B is formed include a second

25　　zwitterionic monomer of the formula VI different from the first zwitterionic monomer.

51.　　A polymer of the formula VIII

30



VIII

in which $X^2$ is selected from the group consisting of Cl, Br, I, $OR^{10}$, $SR^{14}$, $SeR^{14}$, $OP(=O)R^{14}$, $OP(=O)(OR^{14})_2$, $O-N(R^{14})_2$ and $S-C(=S)N(R^{14})_2$, where $R^{10}$ is alkyl of from 1 to 20 carbon atoms in which each of the hydrogen atoms may be independently replaced by halide, $R^{14}$ is aryl or a straight or branched $C_1-C_{20}$ alkyl group, and where an $N(R^{14})_2$ group is present, the two $R^{14}$ groups may be joined to form a 5- or 6-membered heterocyclic ring; and

$R^{11}$, $R^{12}$ and $R^{13}$ are each independently selected from the group consisting of H, halogen, $C_1-C_{20}$ alkyl, $C_3-C_8$ cycloalkyl, $C(=O)R^{15}$, $C(=O)NR^{16}R^{17}$, COCl, OH, CN, $C_2-C_{20}$ alkenyl, $C_2-C_{20}$ alkenyl oxiranyl, glycidyl, aryl, heterocyclyl, aralkyl, aralkenyl, $C_1-C_6$ alkyl in which from 1 to all of the hydrogen atoms are replaced with halogen, $C_1-C_6$ alkyl substituted with from 1 to 3 substituents selected from the group consisting of $C_1-C_4$ alkoxy, aryl, heterocyclyl, $C(=O)R^{15}$, $C(=R)NR^{16}R^{17}$, $-CR^{12}R^{13}X$, oxiranyl and glycidyl;

where $R^{15}$ is alkyl of from 1 to 20 carbon atoms, alkoxy of from 1 to 20 carbon atoms, oligo(alkoxy) in which each alkoxy group has 1 to 5 carbon atoms, aryloxy or heterocyclyloxy any of which groups may have substituents selected from optionally substituted alkoxy, oligoalkoxy, amino (including mono- and di-alkyl amino and trialkyl ammonium, which alkyl groups, in turn may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy) and hydroxyl groups; and $R^{16}$ and $R^{17}$ are independently H or alkyl of from 1 to 20 carbon atoms which alkyl groups, in turn may have substituents selected from acyl, alkoxycarbonyl, alkenoxycarbonyl, aryl and hydroxy, or $R^{16}$ and $R^{17}$ may be joined together to form an alkylene group of from 2 to 5 carbon atoms, thus forming a 3- to 6-membered ring;

such that not more than two of $R^{11}$, $R^{12}$ and $R^{13}$ are H

$M^1$ is the residue of a zwitterionic monomer zwitterionic monomer of the general formula I

$$Y \quad B \quad X \qquad I$$

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,

 and 

A is -O- or $NR^1$;

$A^1$ is selected from a bond, $(CH_2)_n A^2$ and $(CH_2)_n SO_3$- in which n is 1 to 12;

$A^2$ is selected from a bond -O-, O-CO-, CO-O, $CO$-$NR^1$-, -$NR^1$-CO, O-$CO$-$NR^1$-, $NR^1$-CO-O-;

R is hydrogen or $C_{1-4}$ alkyl;

$R^1$ is hydrogen, $C_{1-4}$ alkyl or BX;

$R^2$ is hydrogen or $C_{1-4}$ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents;

X is an ammonium, phosphonium, or sulphonium phosphate or phosphonate ester zwitterionic group;

x is 2 to 500;

$M^2$ is the residue of an ethylenically unsaturated comonomer polymerisable with the zwitterionic monomer; and

y is 0 to 500.

52. A polymer according to claim 51 in which $M^1$ has the formula IX

$$\begin{array}{c} R^{27} \qquad R^{29} \\ | \qquad\quad | \\ \text{—C——C—} \qquad\qquad \text{IX} \\ | \qquad\quad | \\ R^{28} \qquad R^{30}BX \end{array}$$

in which $R^{27}$ is selected from hydrogen $C_{1-4}$ alkyl and groups CO $OR^2$ in which $R^2$ is hydrogen or $C_{1-4}$ alkyl;

$R^{28}$ is selected from hydrogen and $C_{1-4}$ alkyl;

$R^{29}$ is selected from hydrogen, $C_{1-4}$ alkyl and groups CO OR2,

provided that $R^{27}$ and $R^{29}$ are not both CO OR$^2$;

$R^{30}$ is selected from a bond, a group $CH_2A^2$ in which $A^2$ is selected

from a bond, -O-, -O-CO-, -CO-O-, -CO-NR$^1$-, -NR$^1$-CO-, -O-CO-NR$^1$- and -

NR$^1$-CO-O, a group -COA- in which A is -O- or NR$^1$, in which R$^1$ is hydrogen

or $C_{1-4}$ alkyl or BX, and a group -$C_6H_4$-A$^1$- in which A$^1$ is $(CH_2)_nA^2$, a bond or

$(CH_2)_nSO_3$, or $R^{30}$ and $R^{28}$

or $R^{30}$ and $R^{21}$ may be joined to form a group

$$-CO-\overset{|}{N}-CO-$$

where the N atom is joined to B;

and B and X are as defined in claim 51.

53.      A polymer according to claims 51 or claim 52 and 49 in which x

is 5 to 50.

54.      A polymer according to any of claims 51 to 53 in which the

comonomer has the general formula X



in which R$^{31}$ is selected from hydrogen, halogen, $C_{1-4}$ alkyl and groups

COOR$^2$ in which R$^2$ is hydrogen and $C_{1-4}$ alkyl;

$R^{32}$ is selected from hydrogen, halogen and $C_{1-4}$ alkyl;

$R^{33}$ is selected from hydrogen, halogen, $C_{1-4}$ alkyl and groups COOR$^2$

provided that R$^{31}$ and R$^{33}$ are not both COOR$^2$; and

$R^{34}$ is a $C_{1-10}$ alkyl, a $C_{1-20}$ alkoxycarbonyl, a mono-or di-($C_{1-20}$ alkyl)

amino carbonyl, a $C_{6-20}$ aryl (including alkaryl), a $C_{7-20}$ aralkyl, a $C_{6-20}$

aryloxycarbonyl, a $C_{1-20}$ -aralkyloxycarbonyl, a $C_{6-20}$ arylamino carbonyl, a $C_{7-20}$ aralkyl-amino, a hydroxyl or a $C_{2-10}$ acyloxy group, any of which may have

one or more substituents selected from halogen atoms, alkoxy, oligo-alkoxy,

aryloxy, acyloxy, acylamino, amine (including mono and di-alkyl amino and

trialkylammonium in which the alkyl groups may be substituted), carboxyl,

sulphonyl, phosphoryl, phosphino, (including mono- and di- alkyl phosphine and tri-alkylphosphonium), zwitterionic, hydroxyl, vinyloxycarbonyl and other vinylic or allylic, and reactive silyl or silyloxy groups, such as trialkoxysilyl groups;

or $R^{34}$ and $R^{33}$ or $R^{34}$ and $R^{32}$ may together form -$CONR^{35}CO$ in which $R^{35}$ is a $C_{1-20}$ alkyl group.

55. A polymer according to claim 54 in which $R^{31}$ and $R^{32}$ are hydrogen, $R^{33}$ is methyl and $R^{34}$ is a $C_{1-20}$ alkoxycarbonyl, optionally having a hydroxy substituent.

56. A polymer according to any of claims 51 to 55 in which $X^2$ is bromine, $R^{11}$ and $R^{12}$ are each methyl and $R^{13}$ is CO $R^{15}$ in which $R^{15}$ is oligoalkoxy, preferably methoxy-oligoethoxy in which there are 2 to 10 ethoxy groups.

57. A block copolymerisation process in which ethylenically unsaturated monomers are polymerised in the presence of, as initiator, a polymer according to any of claims 51 to 56 and a catalyst.

58. A block copolymerisation process according to claim 57 in which the catalyst is as defined in claim 15.

59. A block copolymerisation process according to claim 58 in which the catalyst is as defined in any of claims 20 to 23.

60. A block copolymerisation process according to any of claims 57 to 59 in which the molar ratio of polymer-initiator to ethylenically unsaturated monomer is in the range 1:(2 to 500), preferably 1:(10 to 50).

61. A macromonomer which is a polymer according to claim 33 having a terminal group comprising an ethylenically unsaturated group.

62. A polymer formed by polymerising by radical polymerisation ethylenically unsaturated monomers including a macromonomer according to claim 61 or a polymer according to claim 41 in which the said functional group comprises an ethylenically unsaturated group.

63. A cross-linked polymer formed by subjecting a polymer according to claim 36 to conditions under which the cross-linkable groups react to cross-link the polymer.

64. Use of a block copolymer according to any of claims 42 to 50 as a drug delivery matrix.

65. A composition comprising a block copolymer according to any of claims 42 to 50 and, absorbed in the copolymer, a drug capable of being released from the copolymer.

66. A composition according claim 65 in which the block copolymer is in the form of a film.

67. A composition according to claim 65 in which the block copolymer is in the form of a dispersion of micelles in an aqueous continuous phase.

68. A pharmaceutical composition comprising a block copolymer according to any of claims 42 to 50 and, absorbed in the copolymer, a drug capable of being released from the copolymer and a pharmaceutical excipient.
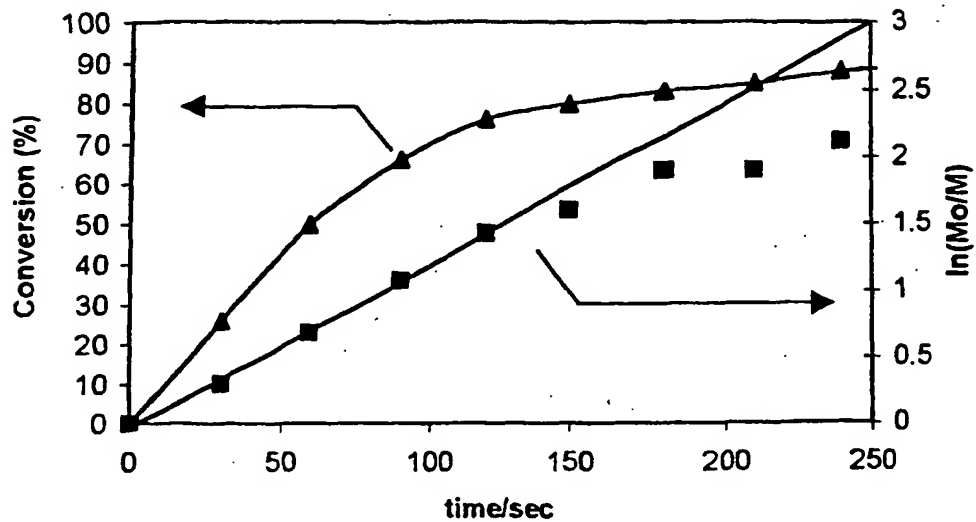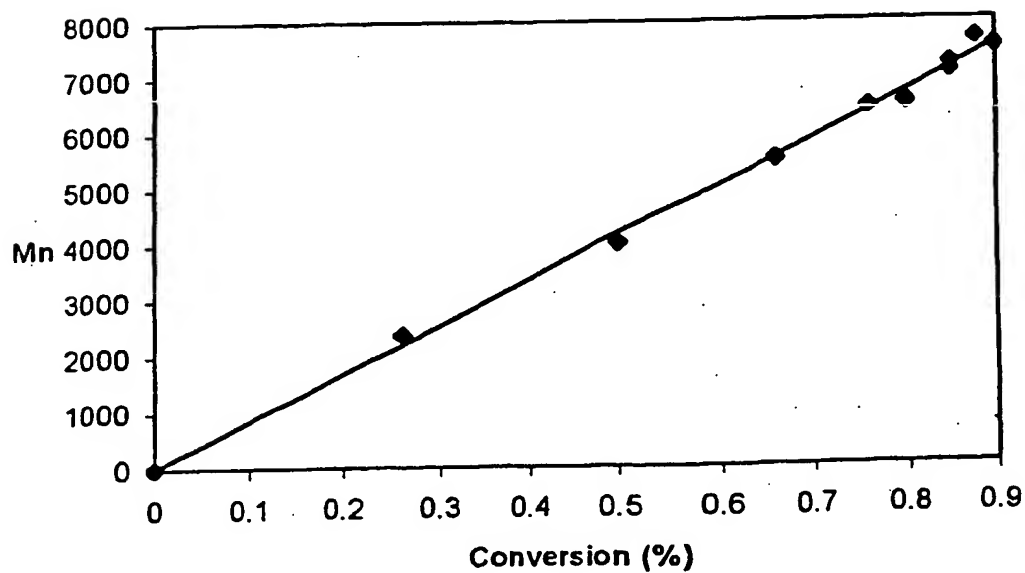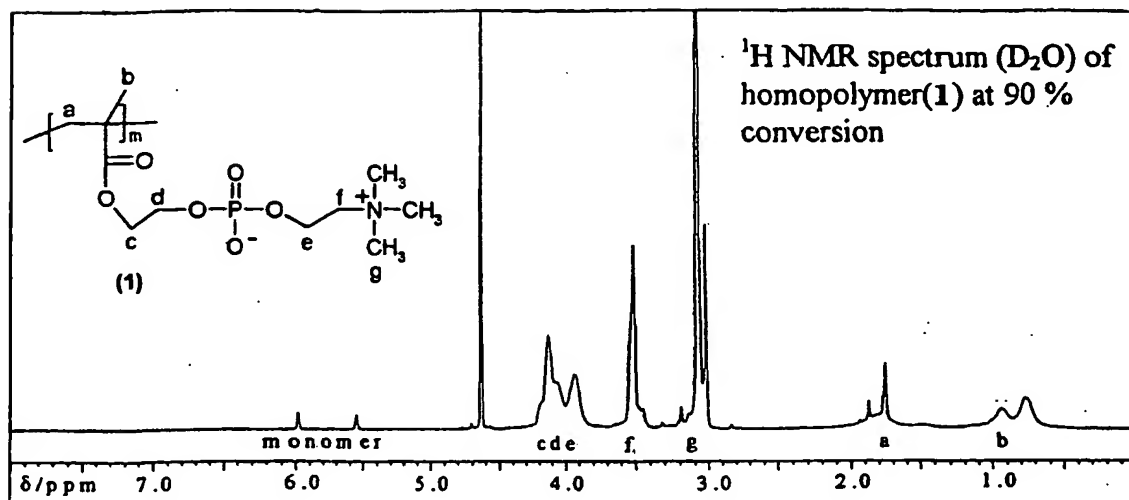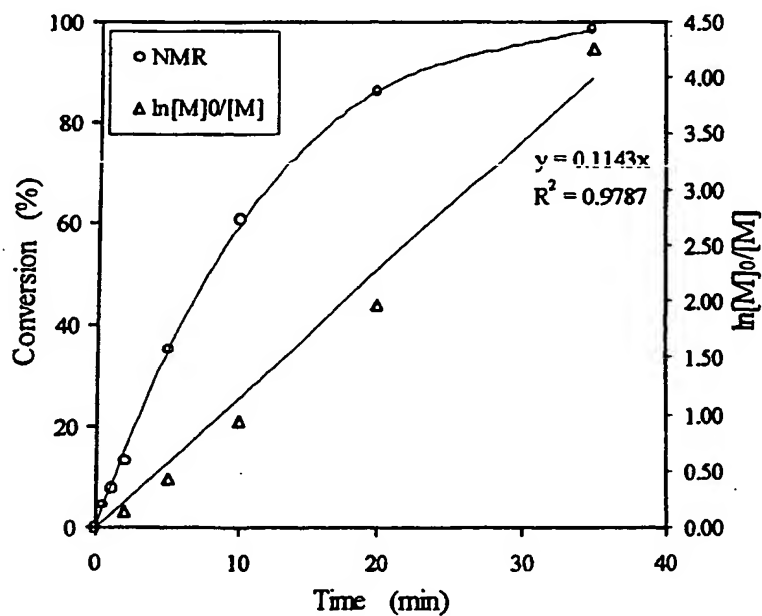
Figure 1



Figure 2
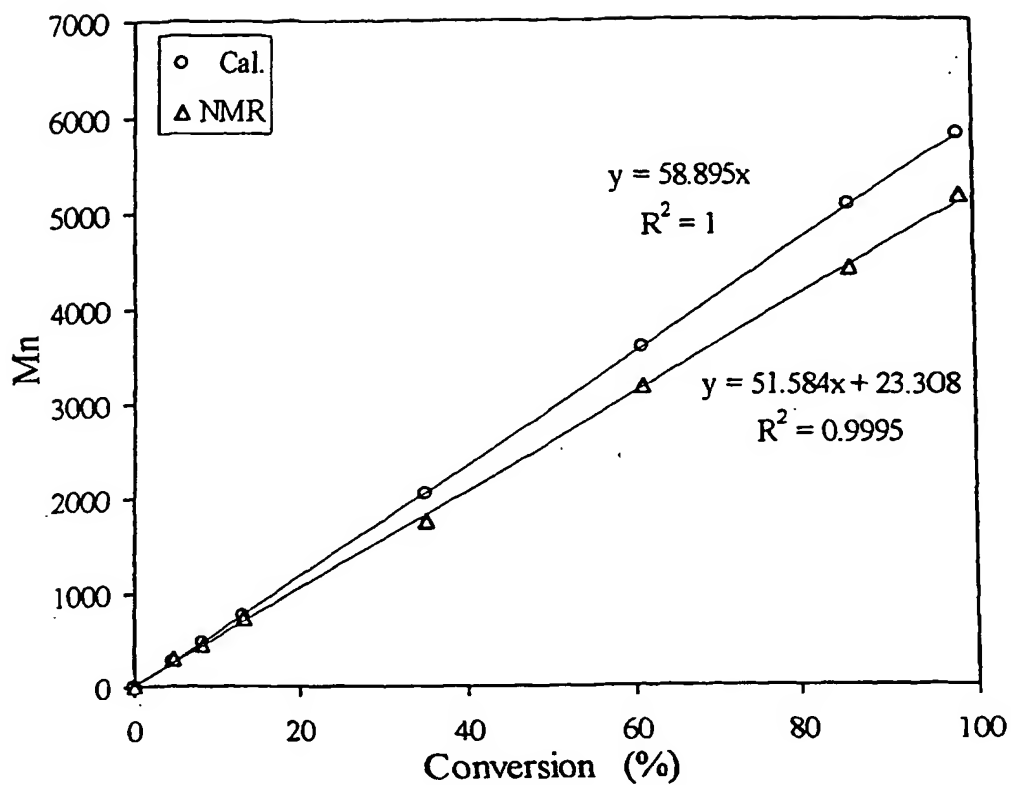
Figure 3
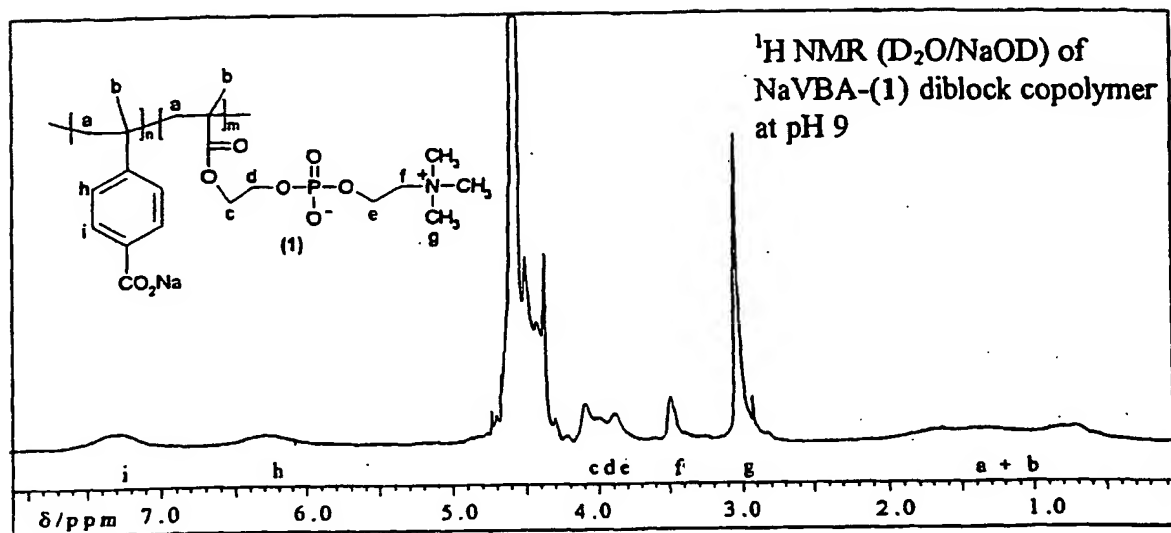


Figure 4
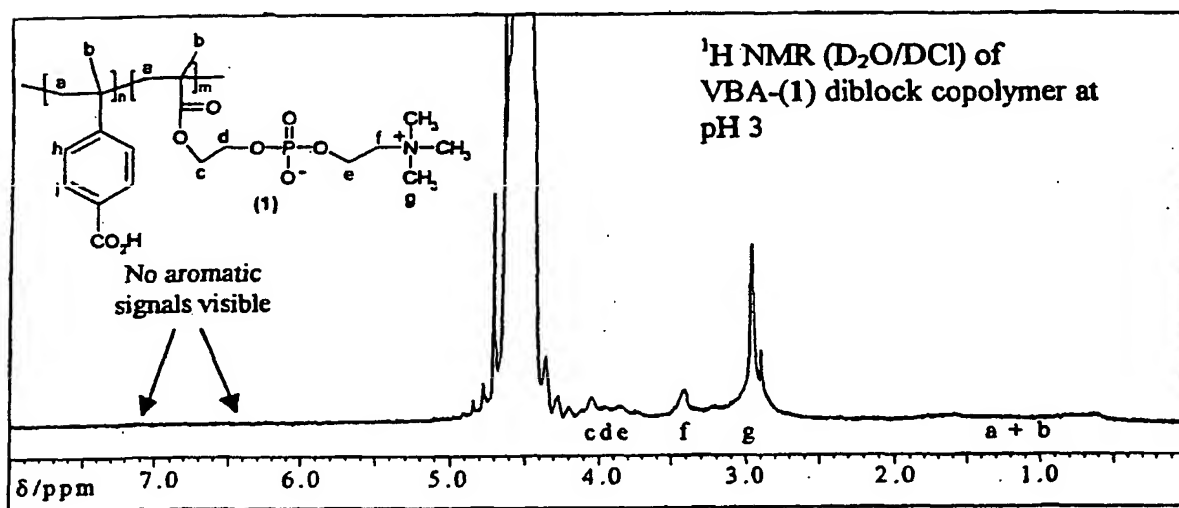
Figure 5

Figure 6



Figure 7
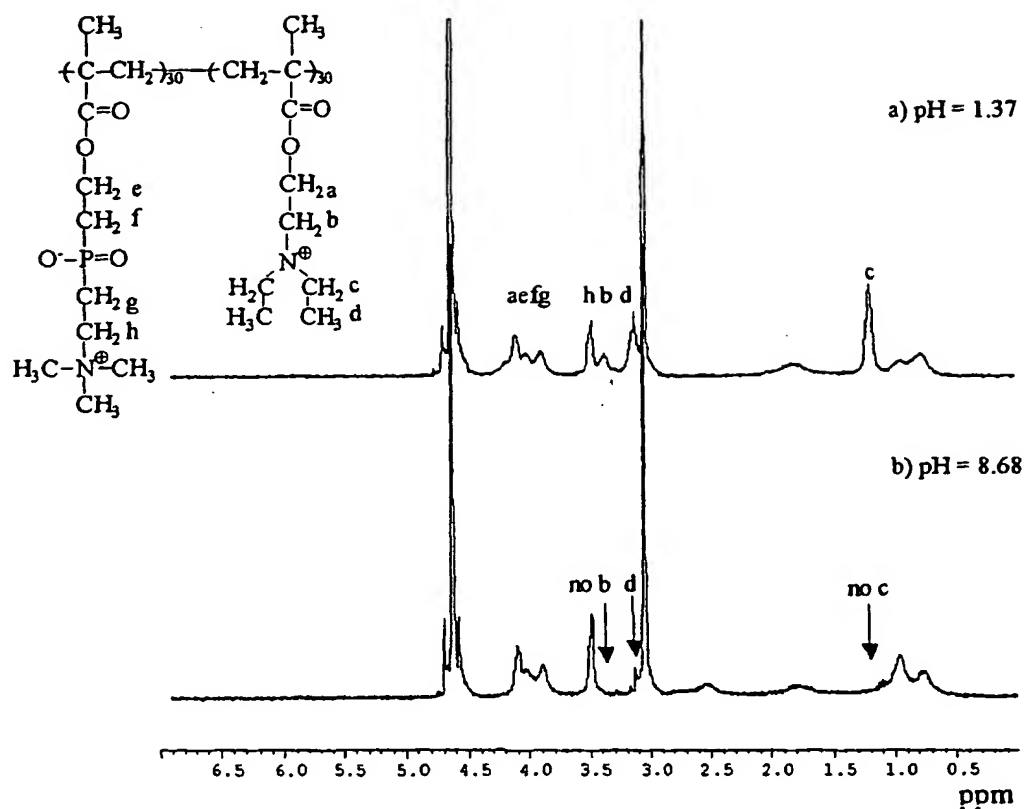
Fig. 8  Proton NMR spectra of Example 24 diblock copolymer obtained in D₂O under the following conditions: a) pH 1.37, b) pH 8.68.
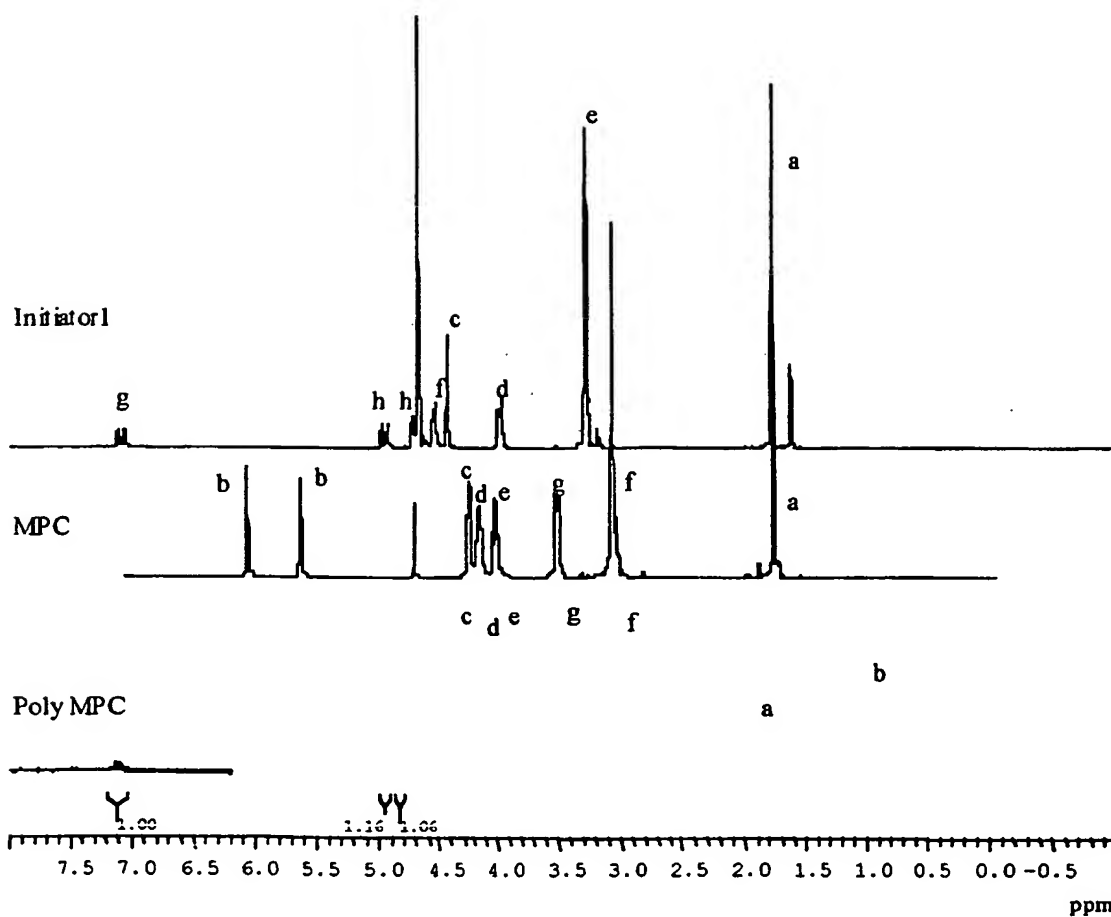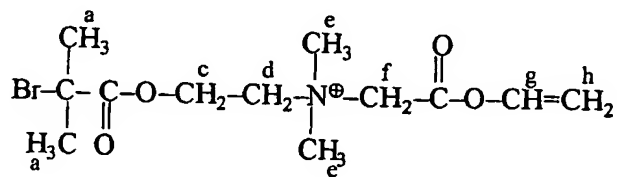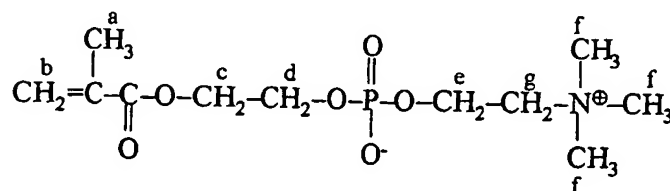
Fig.9    $^1$H NMR spectra of the vinyl acetate-functionalised initiator1, MPC monomer and MPC polymer.

Figure 10

Figure 11
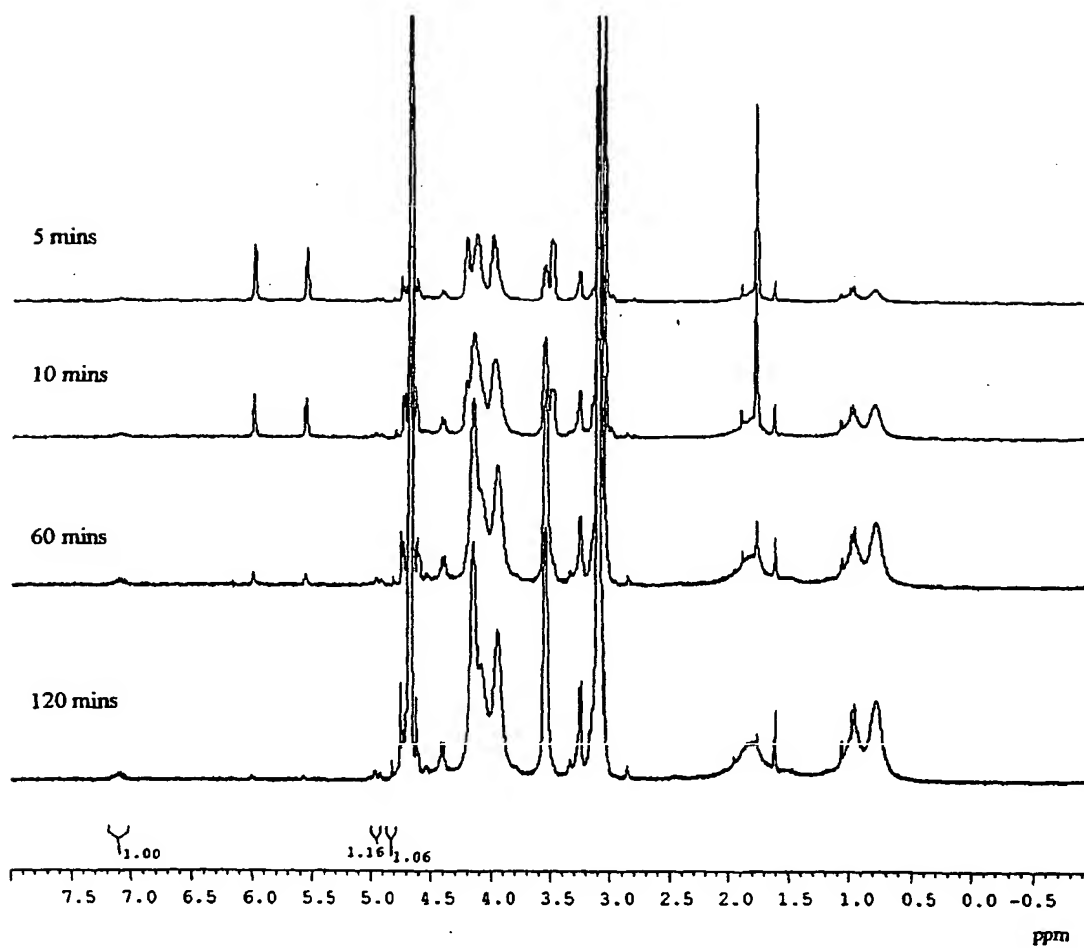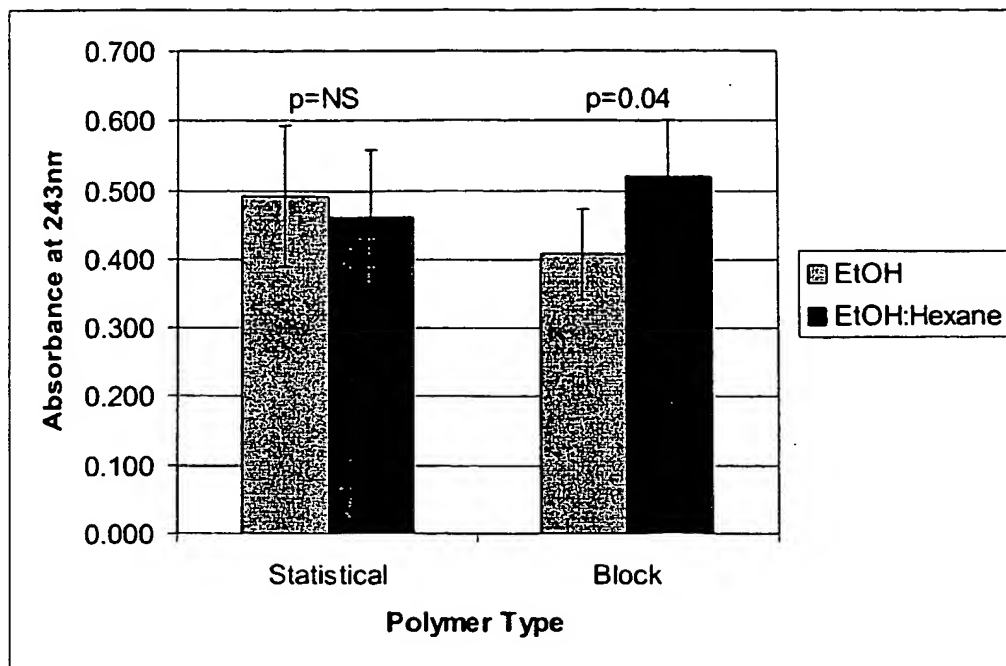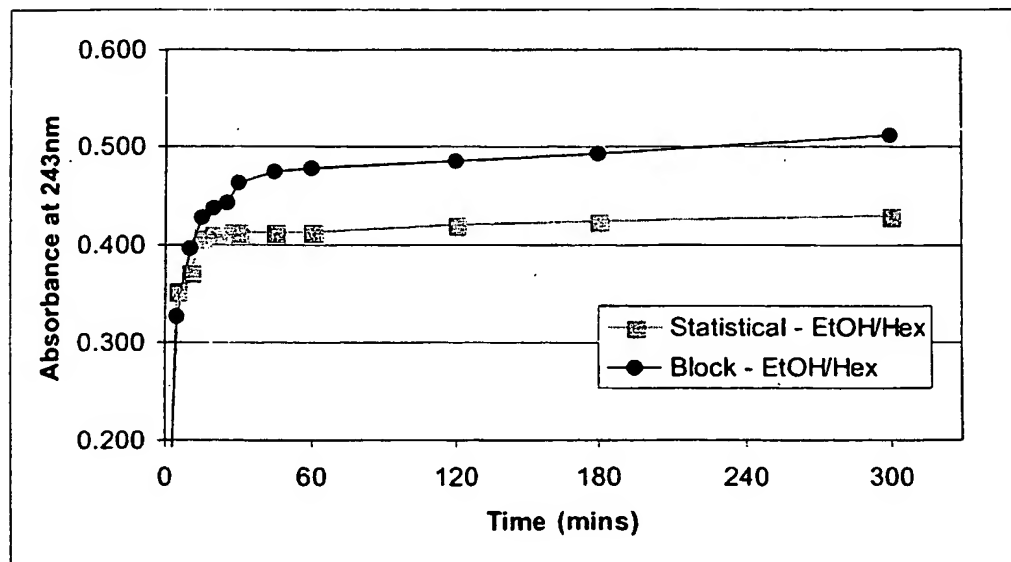


Figure 12

# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER
IPC 7     C08F246/00     C08F4/40      C08F293/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched  (classification system followed by classification symbols)
IPC 7    C08F

Documentation searched other than minimum documentation to the extent that such documents are included  in the fields searched

Electronic data base consulted during the  international search (name of data base and,  where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,  where appropriate,  of the relevant passages | Relevant to claim No. |
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| A | WO 93 01221 A (BIOCOMPATIBLES LTD.)<br>21 January 1993 (1993-01-21)<br>cited in the application<br>--- | |
| A | WO 96 30421 A (MATYJASZEWSKI)<br>3 October 1996 (1996-10-03)<br>cited in the application<br>----- | |

[ ] Further documents are listed in the  continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the  art which is not considered to be of particular relevance

'E' earlier document but published on or after the  international filing date

'L' document which may throw doubts on priority  claim(s) or which is cited to establish the publication date of another citation or other special reason (as  specified)

'O' document referring to an oral disclosure, use,  exhibition or other means

'P' document published prior to the international  filing date but later than the priority date claimed

'T' later document published after the  international filing date or priority date and not in conflict with the  application but cited to understand the principle or theory  underlying the invention

'X' document of particular relevance; the claimed  invention cannot be considered novel or cannot be considered  to involve an inventive step when the document is  taken alone

'Y' document of particular relevance; the claimed  invention cannot be considered to involve an inventive  step when the document is combined with one or more other  such documents. such combination being obvious to a  person skilled in the art.

'&' document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 December 2001 | 03/01/2002 |

| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br><br>Cauwenberg, C |
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